

NOVEL MONO- AND DI-FLUORINATED BENZOTHIOPENE
COMPOUNDS AS INHIBITORS OF APICAL SODIUM CO-DEPENDENT
BILE ACID TRANSPORT (ASBT) AND TAUROCHOLATE UPTAKE

FIELD OF THE INVENTION

- [01] The present invention relates to compounds, pharmaceutical compositions, and methods for treating high blood cholesterol levels in a subject. More particularly, the present invention relates to novel mono-fluorinated or di-fluorinated benzothiopenone compounds that are useful as apical sodium co-dependent bile acid transport (ASBT) inhibitors, pharmaceutical compositions containing the same, methods for making the same and methods for treating hyperlipidemic conditions.

DESCRIPTION OF THE RELATED ART

- [02] The major metabolic fate of cholesterol in the human body is in the hepatic synthesis of bile acids. Bile acids are both passively and actively reabsorbed from the small intestine and recycled via the enterohepatic circulation to conserve the total pool of bile acids. Dietschy, "Mechanisms for the intestinal absorption of bile acids", J. Lipid Res., 9:297-309 (1968). Bile acids undergo passive absorption in the proximal small intestine and active transport in the terminal ileum. Love et al., "New insights into bile acid transport", Curr. Opin. Lipidol., 9(3):225-229 (1998). Ileal active transport accounts for the majority of intestinal bile acid uptake and is the exclusive route for taurine-conjugated bile acids. Id. Ileal active transport is mediated by the apical sodium co-dependent bile acid transporter ("ASBT", also known as the ileal bile acid transporter or "IBAT") localized to the distal one-third of the ileum. Craddock et al., "Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter", Am. J. Physiol., 274 (Gastrointest. Liver Physiol. 37):G157-G169 (1998).
- [03] An equilibrium generally exists between hepatic cholesterol and the bile acid pool. Interruption of the enterohepatic recirculation of bile acids (e.g., the

binding of intestinal bile acids to a sequestering resin such as cholestyramine; the surgical removal of the ileum to physically eliminate ileal ASBT; or the specific inhibition of ileal ASBT) results in a decrease in the liver bile acid pool and stimulates increased hepatic synthesis of bile acids from cholesterol (i.e., an upregulation of cholesterol-7 α -hydroxylase activity), eventually depleting the liver's pool of esterified cholesterol. In order to maintain liver cholesterol levels necessary to support bile acid synthesis, the de novo synthesis of cholesterol increases in the hepatocytes (i.e., an upregulation of 3-hydroxy-3-methylglutaryl coenzyme-A reductase activity) and also increases the uptake of serum cholesterol by upregulating the number of cell surface low density lipoprotein cholesterol receptors ("LDL receptors"). The number of hepatic LDL receptors directly impacts serum low density lipoprotein ("LDL") cholesterol levels, with an increase in the number of LDL receptors resulting in a decrease in serum cholesterol. The net result, therefore, is that serum LDL cholesterol levels decrease when intestinal bile acid reabsorption is reduced.

- [04] A class of antihyperlipidemic agents that operates by inhibiting bile acid reabsorption in the ileum recently has been identified. Examples of this class of agents include the substituted benzothiepines disclosed in U.S. Patent 5,994,391. PCT Patent Application No. WO99/35135 discloses additional substituted benzothiazepine compounds for use as ASBT inhibitors. By way of further example, PCT Patent Application No. WO94/24087 discloses a group of substituted naphthalene compounds for use as ABST inhibitors. The United States Food and Drug Administration, however, has not approved any ASBT inhibitor for use as an antihyperlipidemic agent at this time.
- [05] Numerous antihyperlipidemic agents having other modes of action also have been disclosed in the literature as useful for the treatment of hyperlipidemic conditions and disorders. These agents include, for example, commercially available drugs such as nicotinic acid, bile acid sequestrants including cholestyramine and colestipol, 3-hydroxy-3-methylglutaryl coenzyme-A

reductase inhibitors (“HMG Co-A reductase inhibitors”), probucol, and fibric acid derivatives including gemfibrozil and clofibrate.

- [06] The class of antihyperlipidemic agents known as HMG Co-A reductase inhibitors operates by inhibiting the hepatic enzyme 3-hydroxy-3-methylglutaryl coenzyme-A reductase (“HMG Co-A reductase”). Direct inhibition of HMG Co-A reductase by the monotherapeutic administration of HMG Co-A reductase inhibitors such as pravastatin has been shown to be a clinically effective method of lowering serum LDL cholesterol. Sacks et al., “The Effect of Pravastatin on Coronary Events after Myocardial Infarction in Patients with Average Cholesterol Levels”, New England Journal of Medicine, 335(14):1001-9 (1996). Monotherapeutic treatment with pravastatin may lead to upregulation of cell surface LDL receptors as a mechanism to provide cholesterol to the liver in support of bile acid synthesis. Fujioka et al., “The Mechanism of Comparable Serum Cholesterol Lowering Effects of Pravastatin Sodium, a 3-Hydroxy-3-Methylglutaryl Coenzyme A Inhibitor, between Once- and Twice-Daily Treatment Regimens in Beagle Dogs and Rabbits”, Jpn. J. Pharmacol., Vol. 70, pp. 329-335 (1996).
- [07] The administration of an ASBT inhibitor in combination with an HMG Co-A reductase inhibitor is generally disclosed in PCT Application WO98/40375.
- [08] The treatment of hypercholesterolemia with an HMG Co-A reductase inhibitor in combination with a bile acid sequestering resin also has been reported in the literature. The administration of the HMG Co-A reductase inhibitor lovastatin in combination with the bile acid sequestering resin colestipol is disclosed in Vega et al., “Treatment of Primary Moderate Hypercholesterolemia With Lovastatin (Mevinolin) and Colestipol”, JAMA, Vol. 257(1), pp. 33-38 (1987). The administration of the HMG Co-A reductase inhibitor pravastatin in combination with the bile acid sequestering resin cholestyramine is disclosed in Pan et al., “Pharmacokinetics and pharmacodynamics of pravastatin alone and with cholestyramine in hypercholesterolemia”, Clin. Pharmacol. Ther., Vol. 48, No. 2, pp. 201-207 (August 1990).

- [09] The treatment of hypercholesterolemia with other selected combination regimens also has been reported in the literature. Ginsberg, "Update on the Treatment of Hypercholesterolemia, with a Focus on HMG Co-A Reductase Inhibitors and Combination Regimens", Clin. Cardiol., Vol. 18(6), pp. 307-315 (June 1995), reports that, for resistant cases of hypercholesterolemia, therapy combining an HMG Co-A reductase inhibitor with either a bile acid sequestering resin, niacin or a fibric acid derivative generally is effective and well tolerated. Pasternak et al., "Effect of Combination Therapy with Lipid-Reducing Drugs in Patients with Coronary Heart Disease and 'Normal' Cholesterol Levels", Annals of Internal Medicine, Vol. 125, No. 7, pp. 529-540 (October 1, 1996) reports that treatment with either a combination of the HMG Co-A reductase inhibitor pravastatin and nicotinic acid or a combination of pravastatin and the fibric acid derivative gemfibrozil can be effective in lowering LDL cholesterol levels.
- [10] It is desirable to provide novel ASBT inhibitors that exhibit improved efficacy, improved potency, and/or reduced dosing requirements for the active compounds relative to the specific combination regimens previously disclosed in the published literature.

SUMMARY OF THE INVENTION

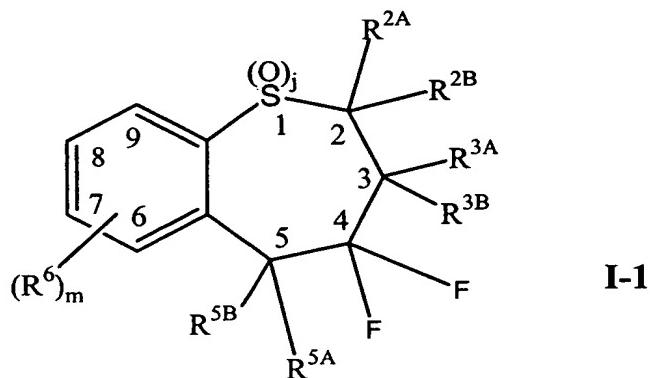
- [11] According to one embodiment, the invention comprises novel fluorinated benzothiepine compounds corresponding to Formulas I-1 to I-24 (see the Detailed Description, *infra*) that are effective agents for the treatment of one or more hyperlipidemic condition(s).
- [12] According to another embodiment, the invention comprises pharmaceutical compositions comprising one or more of the novel fluorinated benzothiepine compounds corresponding to Formulas I-1 to I-24 that are suitable for use in treating one or more hyperlipidemic condition(s).
- [13] According to yet another embodiment, the invention comprises a method for treating one or more hyperlipidemic condition(s) comprising administering to

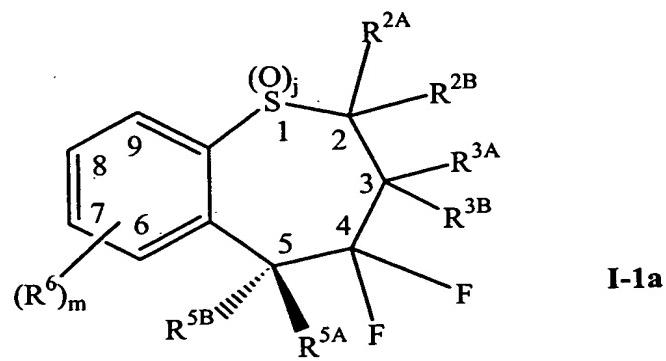
a subject a therapeutically effective amount of one or more of the novel fluorinated benzothiepine compounds corresponding to Formulas I-1 to I-24.

- [14] According to still another embodiment, the invention comprises methods for making the novel benzothiepine compounds corresponding to Formulas I-1 to I-24. Other aspects of the invention will be apparent to those of ordinary skill in view of the present description provided below.

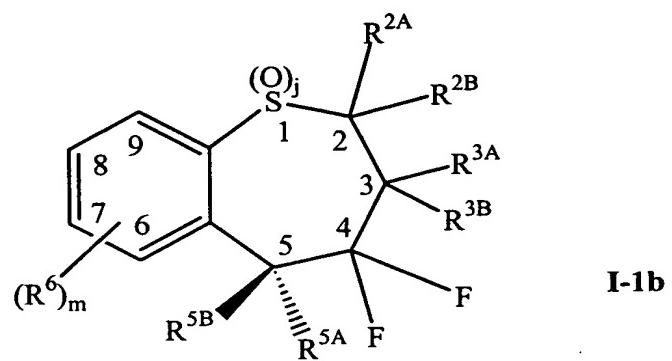
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

- [15] According to one embodiment, the invention comprises novel mono-fluorinated and di-fluorinated benzothiepine compounds defined by Formulas I-1 to I-8:

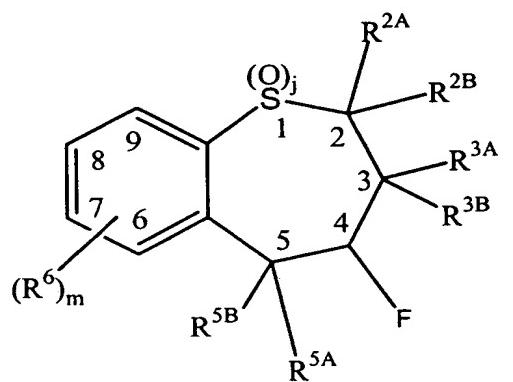




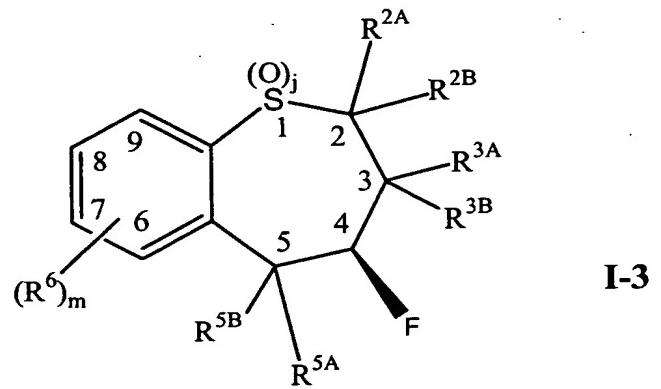
I-1a



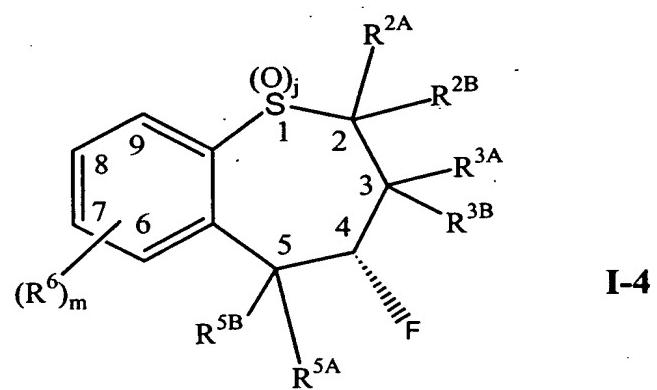
I-1b



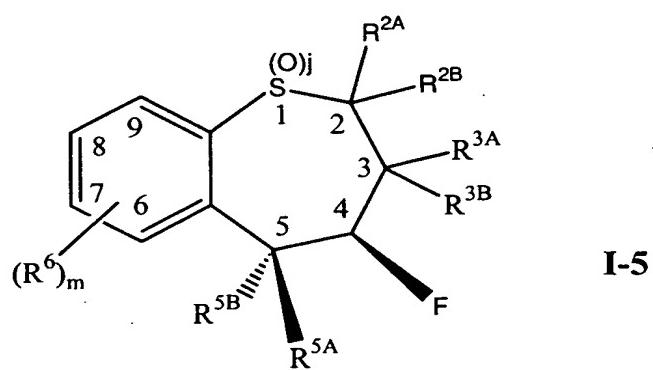
I-2



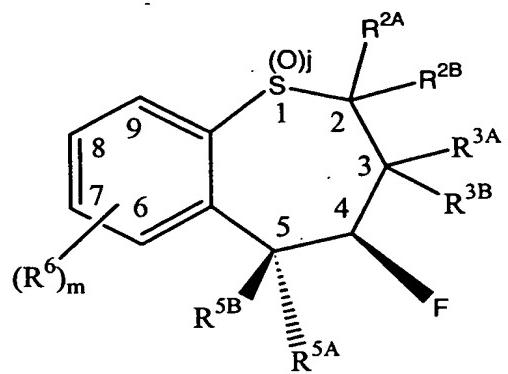
I-3



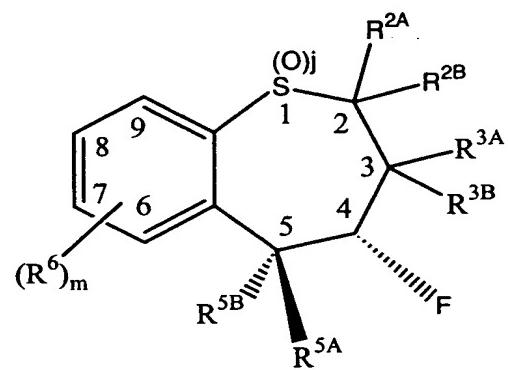
I-4



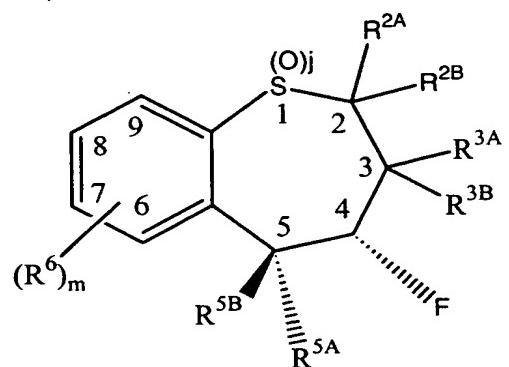
I-5



I-6



I-7



I-8

- [16] or a pharmaceutically acceptable salt, solvate, or prodrug thereof
- [17] wherein j is 0, 1 or 2; m is 0, 1, 2, 3 or 4;
- [18] wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;
- [19] wherein R^{3A}, R^{3B}, R^{5A}, and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl, oxo; aryl-R⁵; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;
- [20] wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;
- [21] wherein R⁵ is selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;
- [22] wherein when R⁵ is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with -NH-X-R or -O-X-R;
- [23] wherein X is selected from the group consisting of -(C=O)_s-alkyl-; -(C=O)_s-alkyl-NH-;-(C=O)_s-alkyl-O-; -(C=O)_s-alkyl-(C=O)_t; and a covalent bond, wherein s and t are independently 0 or 1;
- [24] wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;
- [25] wherein R⁹ and R¹⁰ are as previously defined;
- [26] wherein, when R⁵ ≠ H, R⁵ is optionally substituted with one or more radicals independently selected from the group consisting of halogen; -NO₂; -CN; oxo; hydrocarbyl; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³;

-NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴;
-C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵;
-NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴;
-NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻
; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻;

- [27] wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen and hydrocarbyl;
- [28] wherein A⁻ is a pharmaceutically acceptable anion;
- [29] wherein M is a pharmaceutically acceptable cation;
- [30] wherein one or more R⁶ radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;
- [31] wherein R¹³, R¹⁴, R¹⁵, A⁻, and M are as defined above; and
- [32] wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.
- [33] In one embodiment, aryl-R⁵ is phenyl substituted with -N(H)-X-R³³ or -O-X-R³³ wherein X is selected from the group consisting of:

$-(C=O)s$ -alkyl-; $-(C=O)s$ -alkyl-NH-; $-(C=O)s$ -alkyl-O-; $-(C=O)s$ -alkyl-C=O)t; and a covalent bond; wherein R³³ is selected from selected from the group consisting of monosaccharides,disaccharides, and polysaccharides; and s and t are independently 0 or 1.

- [34] In one embodiment, aryl-R⁵ is phenyl substituted at the para-position with -N(H)-X-R³³ or -O-X-R³³ wherein X is selected from the group consisting of:

$-(C=O)s$ -alkyl-; $-(C=O)s$ -alkyl-NH-; $-(C=O)s$ -alkyl-O-; $-(C=O)s$ -alkyl-C=O)t; and a covalent bond; and wherein R³³ is selected from selected from the group consisting of monosaccharides, disaccharides, and polysaccharides; and s and t are independently 0 or 1.

- [35] In another embodiment, aryl-R⁵ is phenyl substituted at the meta-position with -N(H)-X-R³³ or -O-X-R³³ wherein X is selected from the group consisting of:

- [36] $-(C=O)s$ -alkyl-; $-(C=O)s$ -alkyl-NH-; $-(C=O)s$ -alkyl-O-; $-(C=O)s$ -alkyl-C=O)t; and a covalent bond; and R³³ is selected from selected from the group consisting of monosaccharides,disaccharides, and polysaccharides; and s and t are independently 0 or 1.

- [37] In another embodiment, aryl-R⁵ is phenyl substituted with a radical selected from the group consisting of members (1) – (24), (25) – (48), or (49) – (70), of Table 1 below.

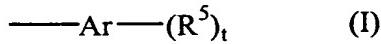
- [38] Furthermore, the term “hydrocarbyl” includes, but is not limited to moieties such as alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl and moieties optionally substituted with aliphatic or cyclic hydrocarbon groups such as alkaryl, alkenaryl and alkynaryl. Typically, the “hydrocarbyl” moieties comprise 1-20 carbon atoms, 1-18 carbon atoms, 1-12 carbon atoms, 3-12 carbon atoms, 1-6 carbon atoms, or 3-6 carbon atoms.

- [39] Also, R^{5A} and R^{5B} may be independently selected from the group consisting of hydrogen, aryl, heterocycle, quaternary heterocycle and quaternary heteroaryl wherein said aryl, heteroaryl, quaternary heterocycle, and quaternary

heteroaryl can be substituted with one or more substituent groups independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR¹³, NR¹³R¹⁴, SR¹³, S(O)R¹³, SO₂R¹³, SO₃R¹³, NR¹³OR¹⁴, NR¹³NR¹⁴R¹⁵, NO₂, CO₂R¹³, CN, OM, SO₂OM, SO₂NR¹³R¹⁴, C(O)NR¹³R¹⁴, C(O)OM, COR¹³, P(O)R¹³R¹⁴, P⁺R¹³R¹⁴R¹⁵A⁻, P(OR¹³)OR¹⁴, S⁺R¹³R¹⁴A⁻, and N⁺R⁹R¹¹R¹²A⁻;

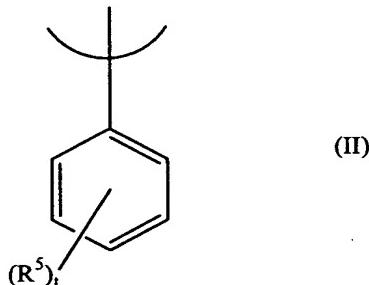
- [40] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR⁷, N⁺R⁷R⁸A⁻, S, SO, SO₂, S⁺R⁷A⁻, PR⁷, P(O)R⁷, P⁺P⁷R⁸A⁻, or phenylene;
- [41] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR⁷, NR⁷R⁸, SR, S(O)R⁷, SO₂R⁷, SO₃R⁷, CO₂R⁷, CN, oxo, CONR⁷R⁸, N⁺R⁷R⁸R⁹A⁻, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, P(O)R⁷R⁸, P⁺R⁷R⁸A⁻, and P(O)(OR⁷)OR⁸ wherein R⁷ and R⁸ are independently selected from hydrogen and alkyl.

- [42] Even further, R^{5A} and R^{5B} may independently have the formula (I):



- [43] wherein t is an integer selected from 0, 1, 2, 3, 4 and 5;
- [44] wherein Ar is selected from the group consisting of phenyl, thiophenyl, pyridyl, piperazinyl, piperonyl, pyrrolyl, naphthyl, furanyl, anthracenyl, quinolinyl, isoquinolinyl, quinoxaliny, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyrimidinyl, thiazolyl, triazolyl, isothiazolyl, indolyl, benzoimidazolyl, benzoxazolyl, benzothiazolyl, and benzoisothiazolyl;

- [45] wherein one or more R^5 are independently selected from the group consisting of alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, heterocycle, arylalkyl, halogen, oxo, OR^{13} , $NR^{13} R^{14}$, SR^{13} , $S(O)R^{13}$, $SO_2 R^{13}$, $SO_3 R^{13}$, $NR^{13} OR^{14}$, $NR^{13} NR^{14} R^{15}$, NO_2 , $CO_2 R^{13}$, CN , OM , $SO_2 OM$, $SO_2 NR^{13} R^{14}$, $C(O)NR^{13} R^{14}$, $C(O)OM$, CR^{13} , $P(O)R^{13} R^{14}$, $P^+ R^{13} R^{14} R^{15} A^-$, $P(OR^{13})OR^{14}$, $S^+ R^{13} R^{14} A^-$, and $N^+ R^9 R^{11} R^{12} A^-$;
- [46] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can be further substituted with one or more substituent groups selected from the group consisting of OR^7 , $NR^7 R^8$, SR^7 , $S(O)R^7$, $SO_2 R^7$, $SO_3 R^7$, $CO_2 R^7$, CN , oxo, $CONR^7 R^8$, $N^+ R^7 R^8 R^9 A^-$, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocycle, arylalkyl, quaternary heterocycle, quaternary heteroaryl, $P(O)R^7 R^8$, $P^+ R^7 R^8 A^-$, and $P(O)(OR^7)OR^8$;
- [47] wherein said alkyl, alkenyl, alkynyl, polyalkyl, polyether, aryl, haloalkyl, cycloalkyl, and heterocycle can optionally have one or more carbons replaced by O, NR^7 , $N^+ R^7 R^8 A^-$, S, SO, SO_2 , $S^+ R^7 A^-$, PR^7 , $P(O)R^7$, $P^+ R^7 R^8 A^-$, or phenylene; and
- [48] wherein t and R^5 are as previously described.
- [49] Yet, even further, R^{5A} and R^{5B} may independently have the formula (II):



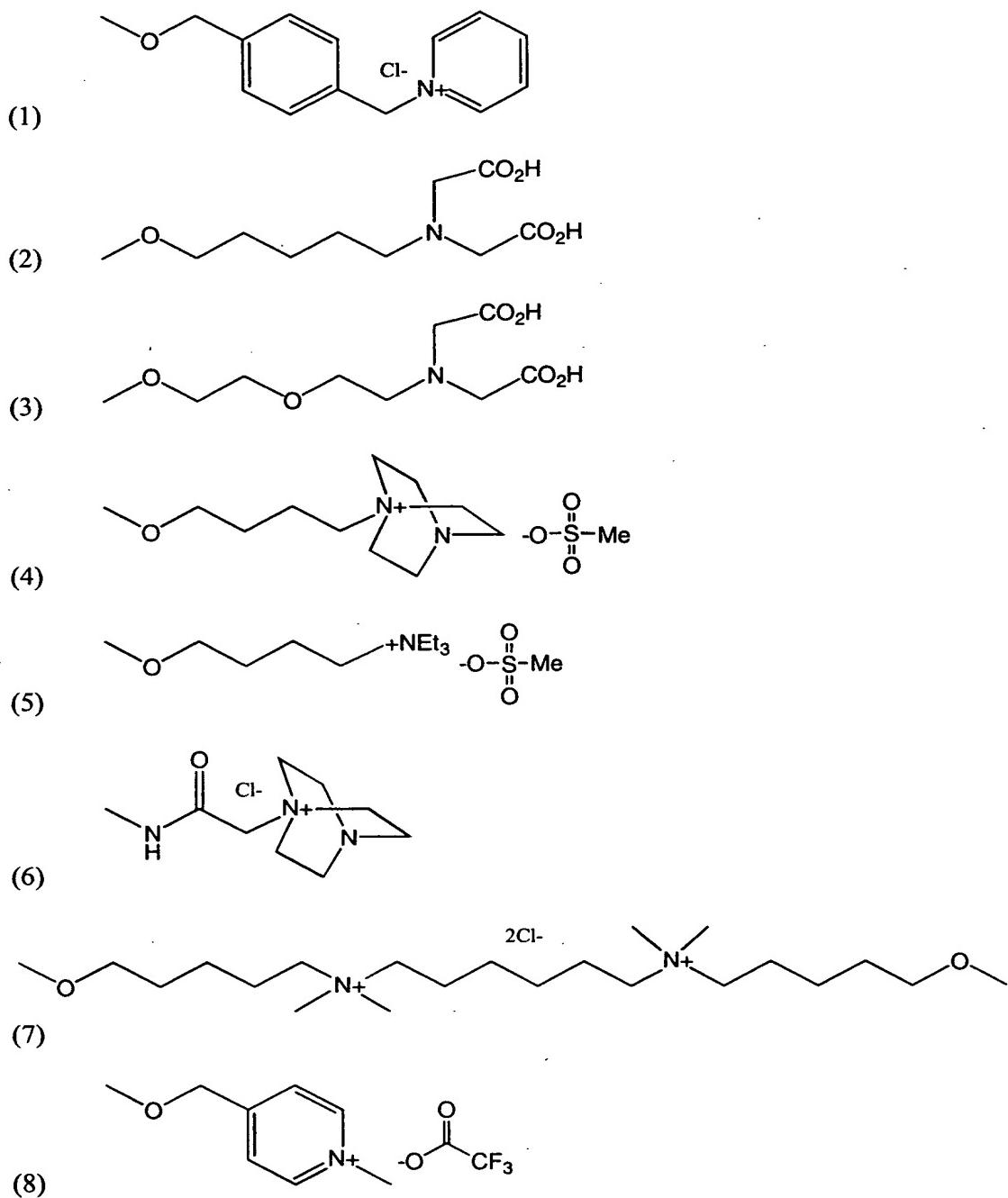
wherein t and R^5 are as previously described.

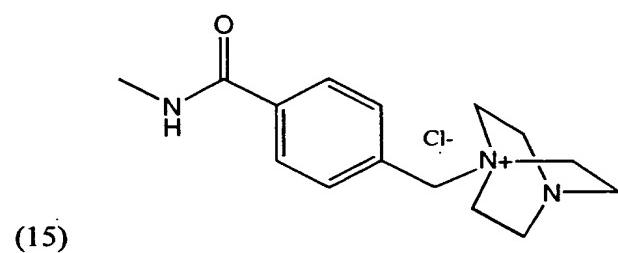
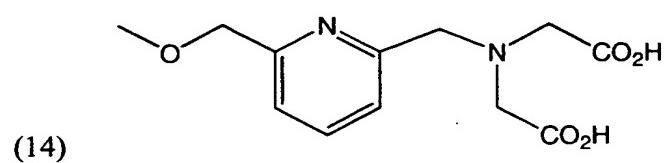
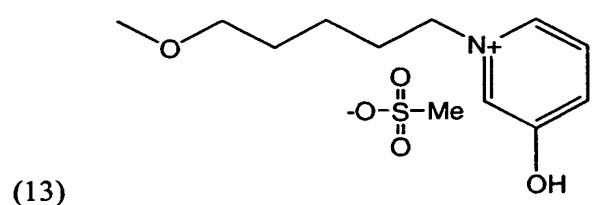
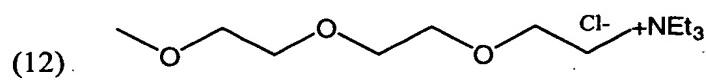
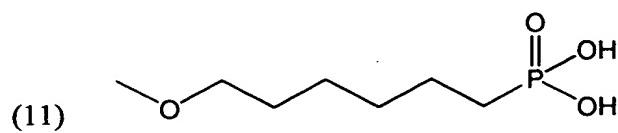
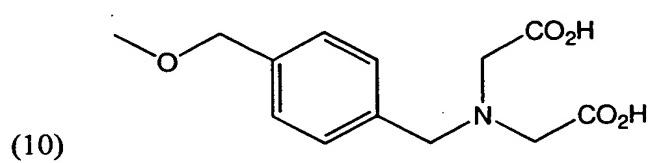
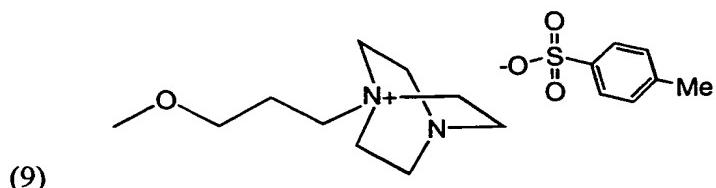
- [50] Furthermore, one or more R⁶ radicals are in the 6-, 7-, 8- and/or 9- position of the benzo ring of formulas I-1 to I-24 described herein. Preferably, R⁶ is in the 7-, 8- and/or 9- position of the benzo ring of formulas I-1 to I-24. More preferably, R⁶ is in the 7- and/or 8- position of the benzo ring of formulas I-1 to I-24. Furthermore, R⁶ is independently selected from the group consisting of:
- [51] (a) alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR¹³, NR¹³ R¹⁴, NR¹³ NR¹⁴ R¹⁵, N⁺ R⁹ R¹¹ R¹² A⁻, SR¹³, S⁺ R¹³ R¹⁴, CO₂ R¹³, NR¹⁴ C(O)R¹³, and NR¹⁴ C(O)R¹³, wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR⁹, NR⁹ R¹⁰, N⁺ R⁹ R¹⁰ R¹² A⁻, SR⁹, S(O)R⁹, SO₂ R⁹, SO₃ R⁹, oxo, CO₂ R⁹, CN, halogen, CONR⁹ R¹⁰ SO₂ OM, SO₂ NR⁹ R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺ R⁹ R¹¹ R¹² A⁻, S⁺ R⁹ R¹⁰ A⁻, or C(O)OM;
- [52] wherein in R⁶, one or more carbons are optionally replaced by O, NR¹³, N⁺ R¹³ R¹⁴ A⁻, S, SO, SO₂, S⁺ R¹³ A⁻, PR¹³, P(O)R¹³, P⁺ R¹³ R¹⁴ A⁻, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl, and
- [53] wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR⁹, N⁺ R⁹ R¹⁰ A⁻, S, SO, SO₂, S⁺ R⁹ A⁻, PR⁹, P⁺ R⁹ R¹⁰ A⁻, or P(O)R⁹;
- [54] (b) alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, polyether, halogen, OR¹³, NR¹³ R¹⁴, NR¹³ NR¹⁴ R¹⁵, N⁺ R⁹ R¹¹ R¹² A⁻, SR¹³, S⁺ R¹³ R¹⁴, CO₂ R¹³, NR¹⁴ C(O)R¹³, and NR¹⁴ C(O)R¹³;
- [55] wherein alkyl, aryl, cycloalkyl, heterocycle, polyalkyl, acyloxy, and polyether, can be further substituted with OR⁹, NR⁹ R¹⁰, N⁺ R⁹ R¹¹ R¹² A⁻, SR⁹, S(O)R⁹, SO₂ R⁹, SO₃ R⁹, oxo, CO₂ R⁹, CN, halogen, CONR⁹ R¹⁰ SO₂ OM, SO₂ NR⁹ R¹⁰, PO(OR¹⁶)OR¹⁷, P⁺ R⁹ R¹¹ R¹² A⁻, S⁺ R⁹ R¹⁰ A⁻, or C(O)OM;

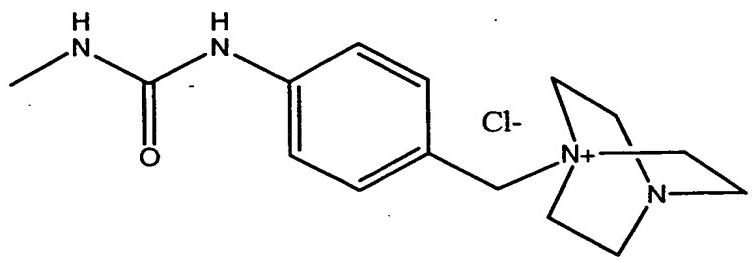
- [56] wherein R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{12} , R^{13} , R^{14} , R^{15} and A^- are as previously defined and R^{16} and R^{17} are independently selected from the group consisting of hydrogen and alkyl, and optionally $R^{13} = R^{14} =$ methyl;
- [57] wherein in R^6 , one or more carbons are optionally replaced by O, NR^{13} , N^+R^{13} $R^{14}A^-$, S, SO, SO_2 , $S^+R^{13}A^-$, PR^{13} , $P(O)R^{13}$, $P^+R^{13}R^{14}A^-$, phenylene, amino acid, peptide, polypeptide, carbohydrate, polyether, or polyalkyl; and
- [58] wherein in said polyalkyl, phenylene, amino acid, peptide, polypeptide, and carbohydrate, one or more carbons are optionally replaced by O, NR^9 , N^+R^9 $R^{10}A^-$, S, SO, SO_2 , $S^+R^9A^-$, PR^9 , $P^+R^9R^{10}A^-$, or $P(O)R^9$;
- [59] (c) polyether, OR^{13} , $NR^{13}R^{14}$ and $N^+R^9R^{11}R^{12}A^-$;
- [60] (d) polyether, OR^{13} and $NR^{13}R^{14}$.
- [61] According to another embodiment, the class of ASBT inhibitor compounds are as previously defined by Formulas I-1 to I-8 except that:
- [62] j is 2;
- [63] R^{2A} and R^{2B} are hydrogen;
- [64] wherein R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen and alkyl; and
- [65] wherein R^{5A} and R^{5B} are independently selected from the group consisting of hydrogen and phenyl optionally substituted at the meta or para position with R^5 selected from the group consisting of members (1) – (70) denoted in Table 1 below. It is noted that when R^5 is a bridging linkage, dimeric or polymeric compounds of the type {-benzothiepene-bridge-benzothiepene-} are formed wherein the benzothiepene is selected from the group consisting of Formulas I-1 to I-24 and exemplary bridging R^5 groups include, but are not limited to, (7), (17) and (24) in Table 1 below.

TABLE 1

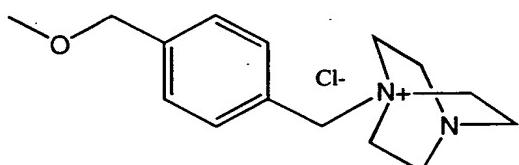
R⁵



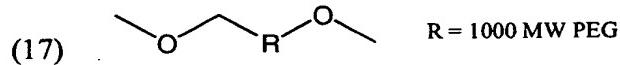




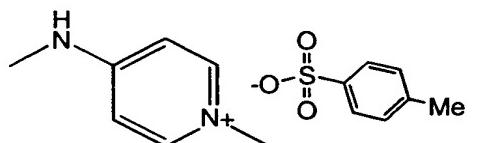
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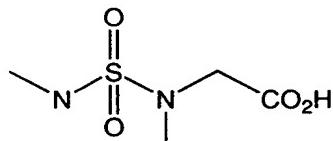
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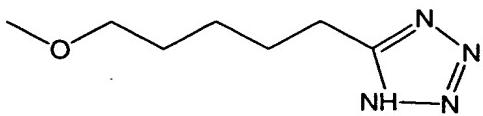
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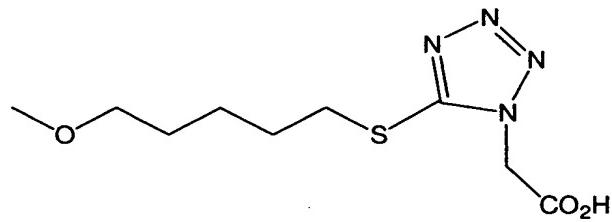
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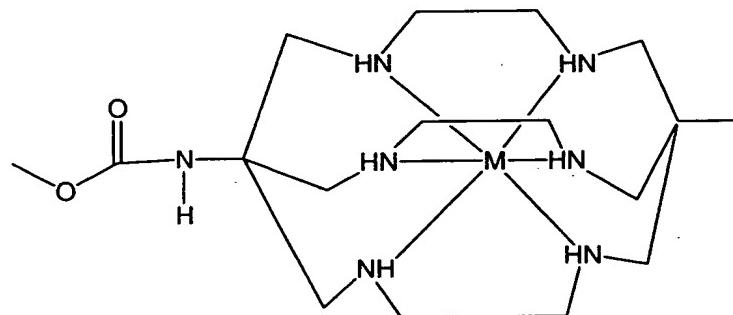
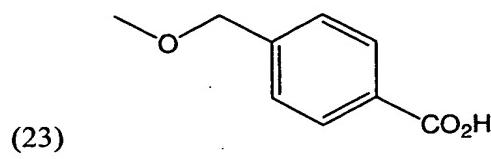
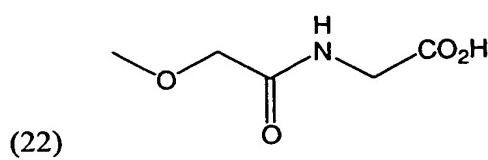
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(20)

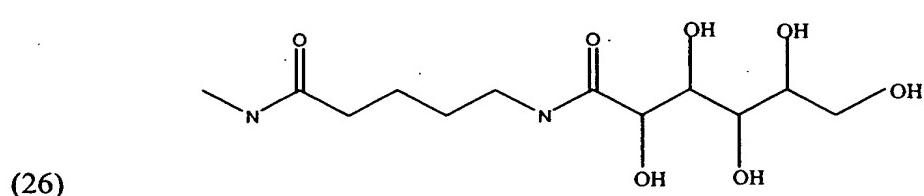
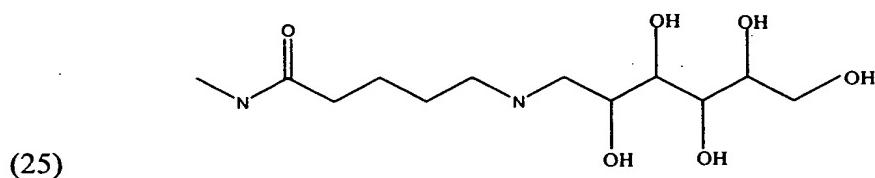


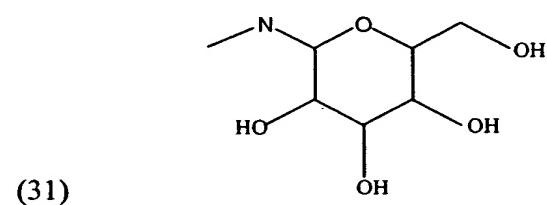
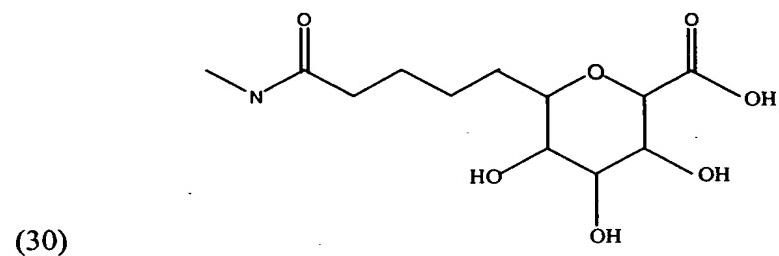
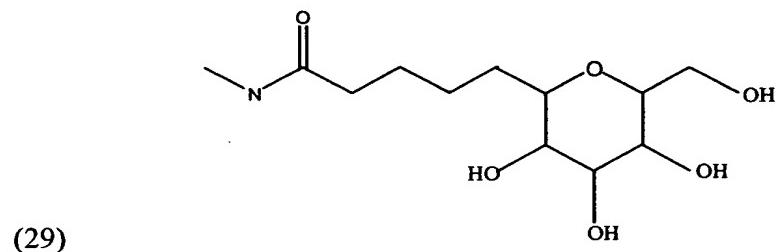
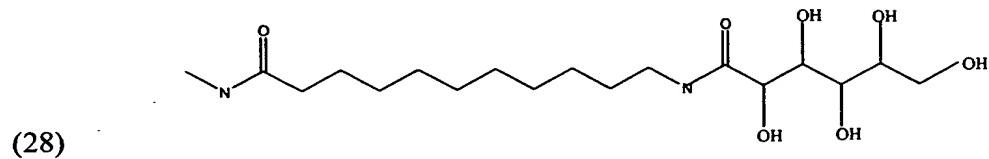
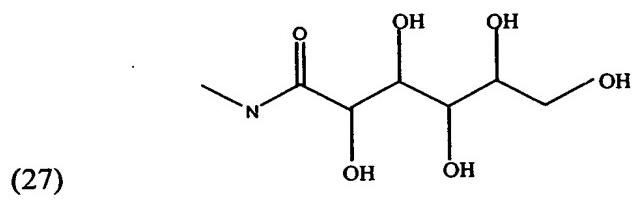
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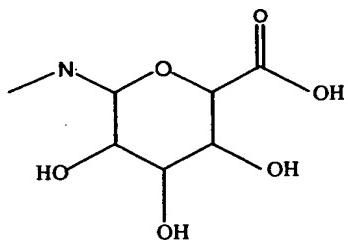


(24)

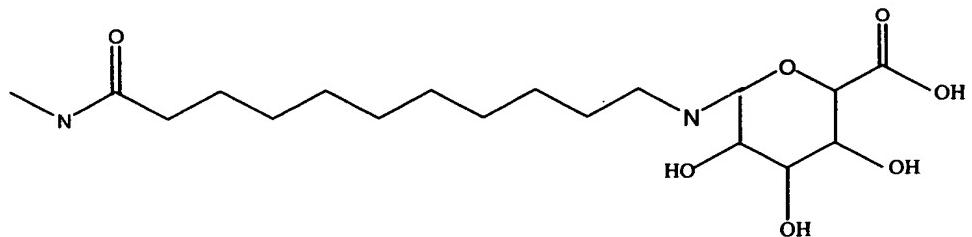
$M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}



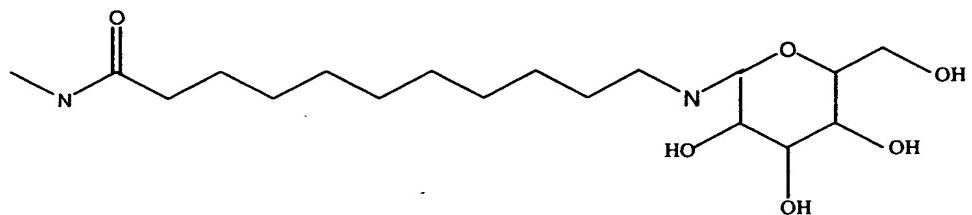




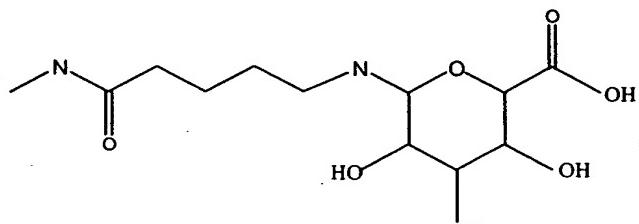
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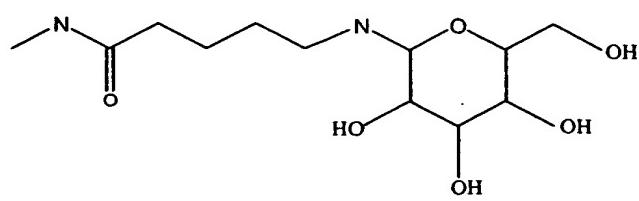
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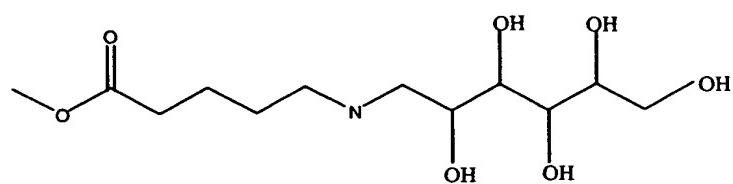
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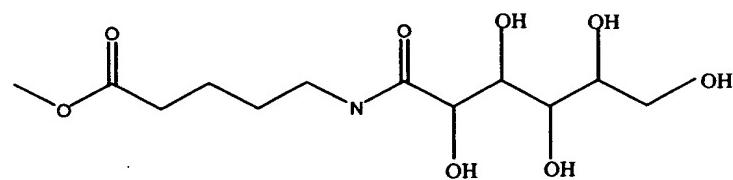
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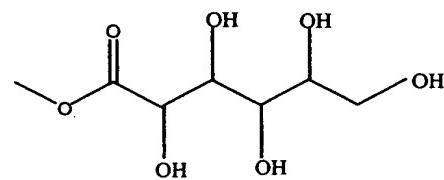
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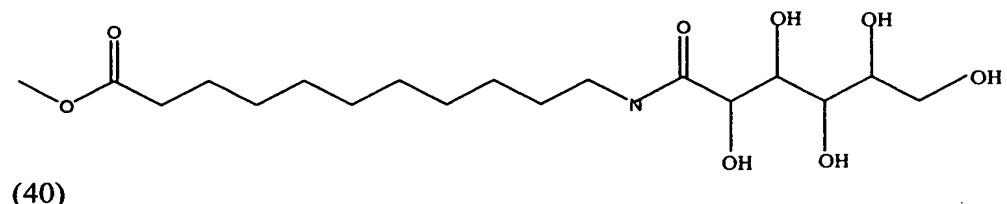
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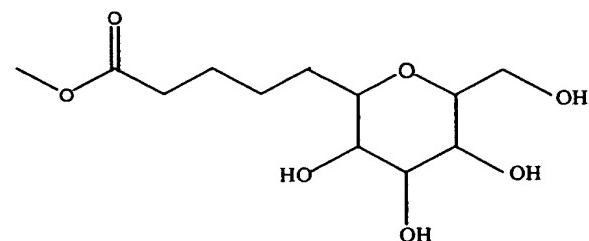
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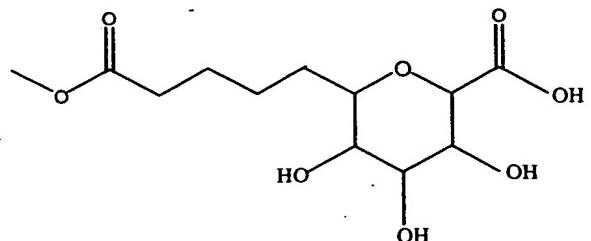
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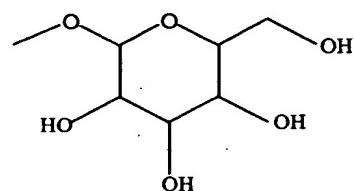
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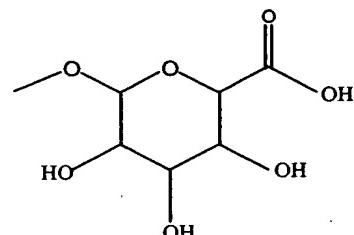
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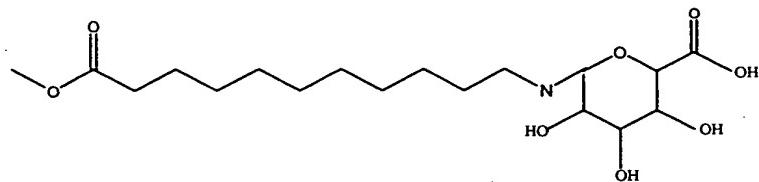
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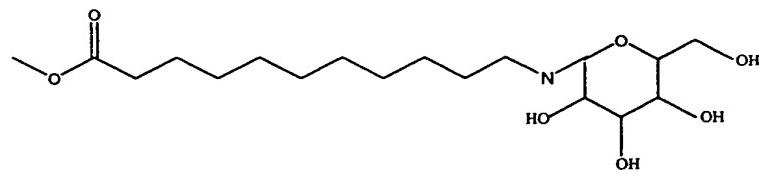
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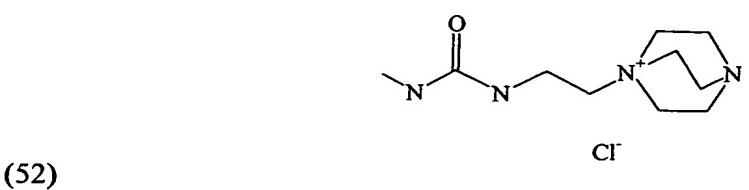
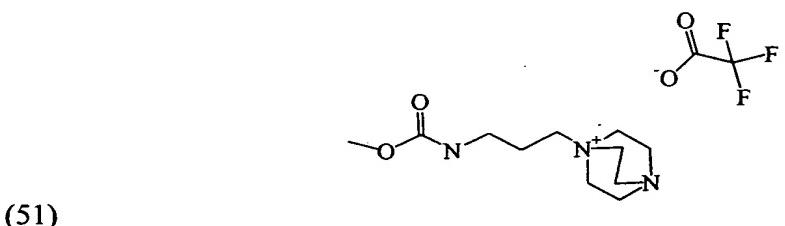
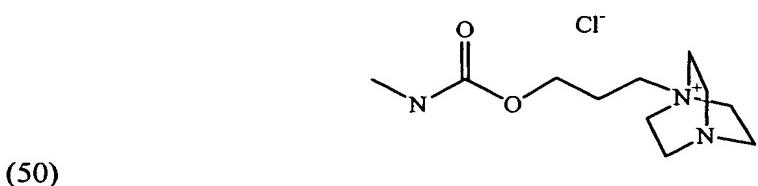
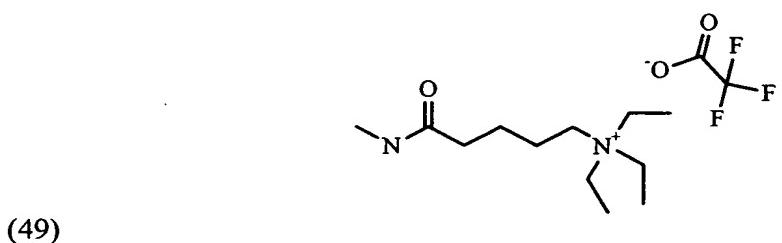
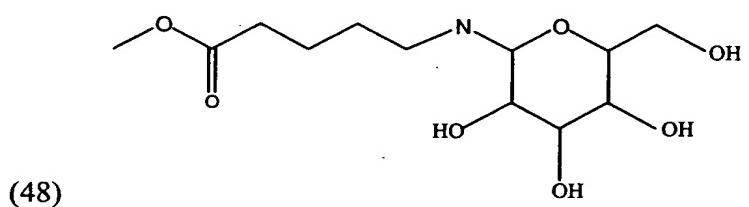
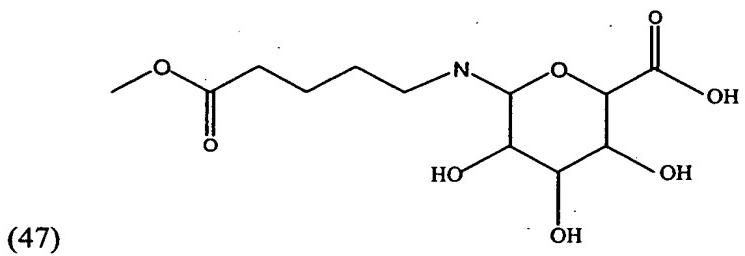
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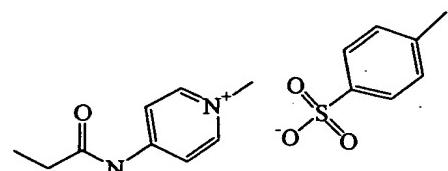


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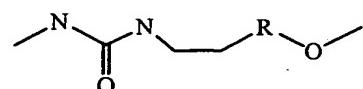


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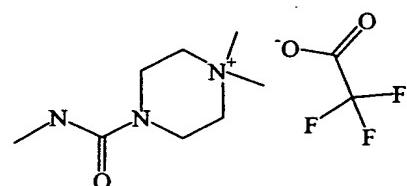




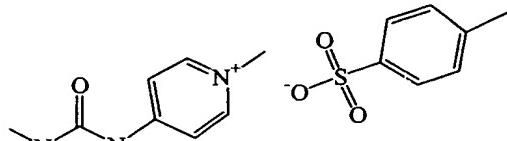
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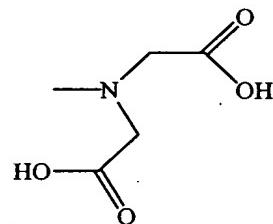
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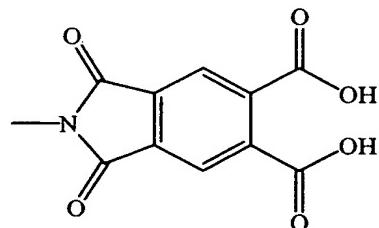
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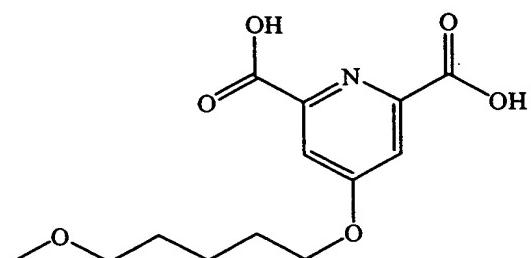
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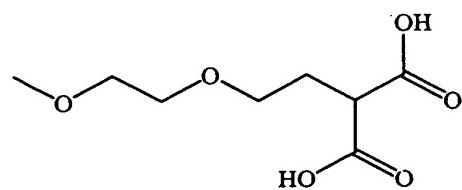
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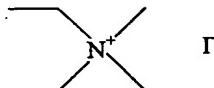
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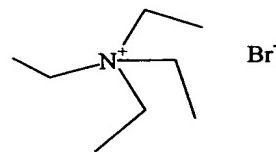
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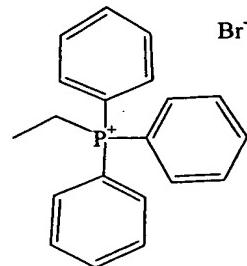
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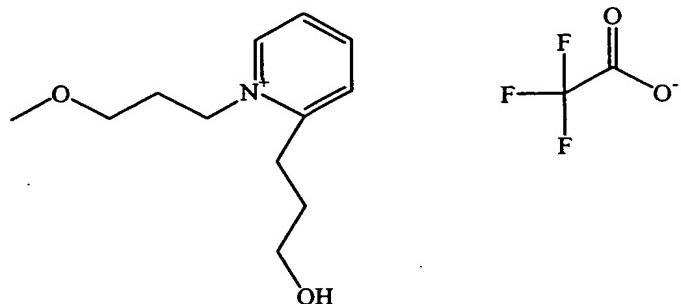
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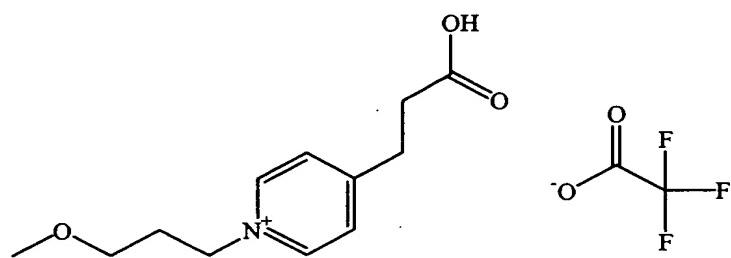
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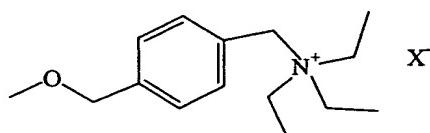
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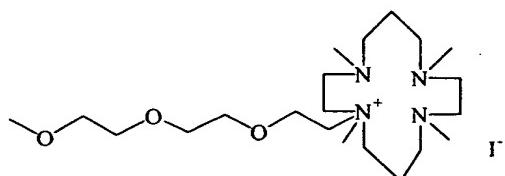
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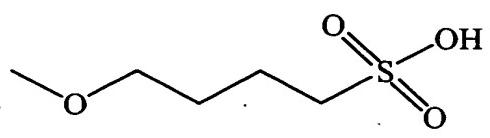
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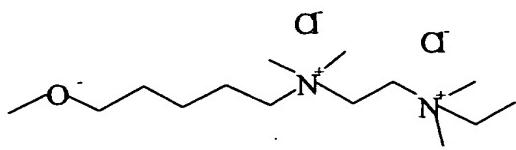
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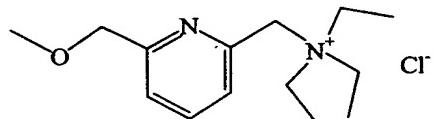
(67)



(68)

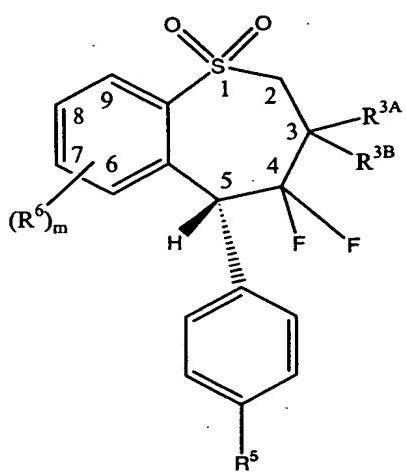


(69) and

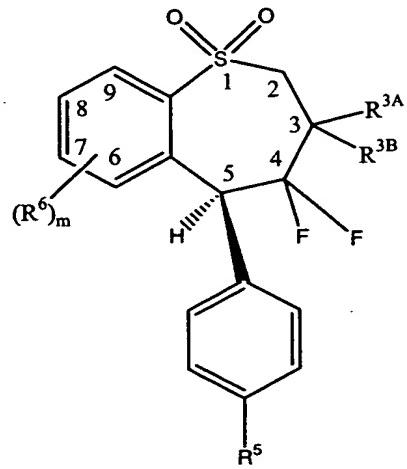


(70)

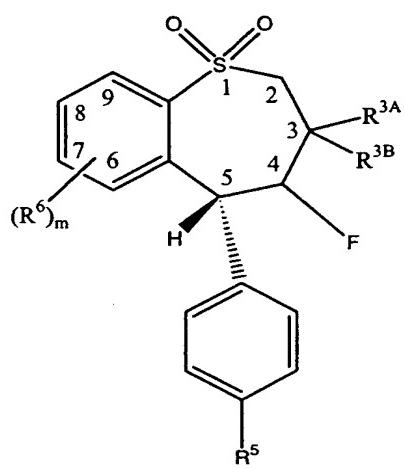
- [66] Also, in tails (1) – (70) the specified anion may be replaced by another pharmaceutically acceptable anion (e.g., A⁻ which anion is as previously described). Optionally, R⁵ may be selected from the following: (1) – (24), (25) – (48) or (49) – (70) from Table 1. Further, R⁵ may be acidic or contain a quarternary ammonium nitrogen. Even further, R⁵ may be selected from the following: (1) – (5), (6) – (10), (11) – (15), (16) – (20), (21) – (25), (26) – (30), (31) – (35), (36) – (40), (41) – (45), (46) – (50), (51) – (55), (56) – (60), (61) – (65), (66) – (70), or combinations thereof from Table 1.
- [67] Other exemplary embodiments of ASBT inhibitors of the present invention are represented by Formulas I-9 to I-16 below.



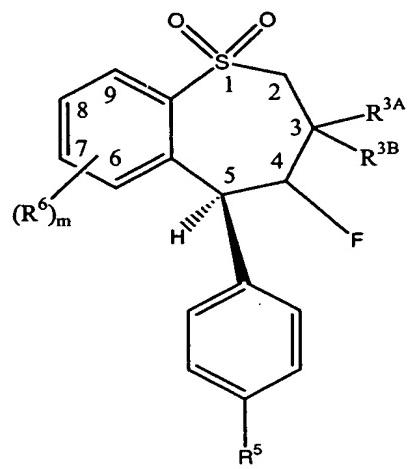
I-9



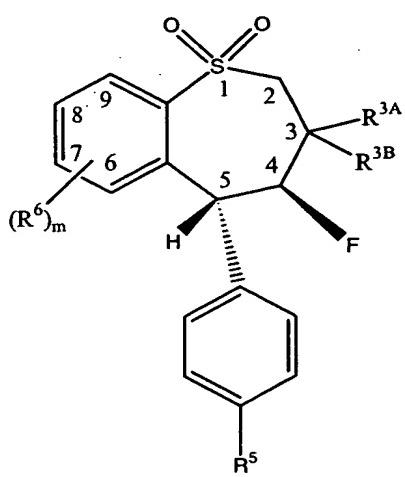
I-10



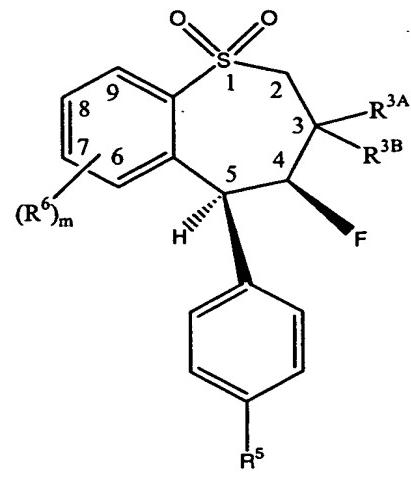
I-11



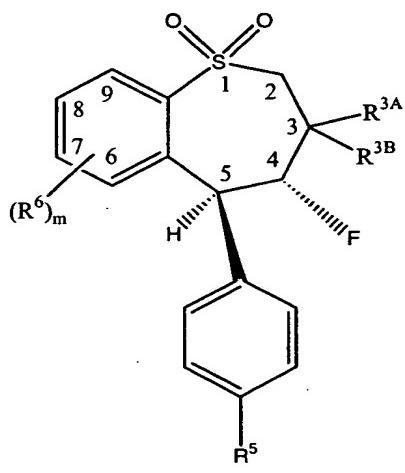
I-12



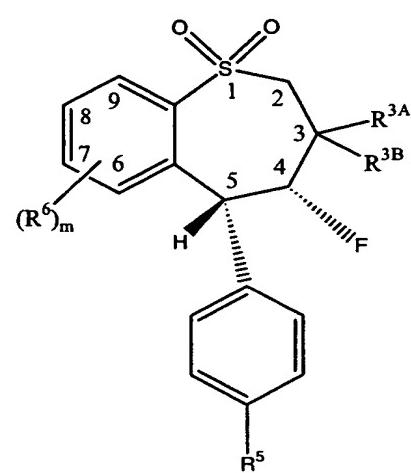
I-13



I-14



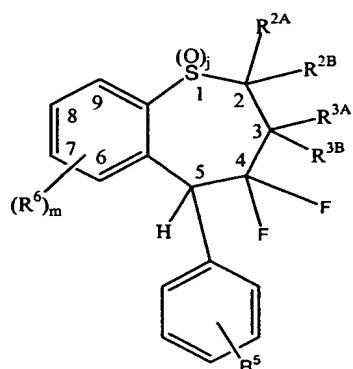
I-15



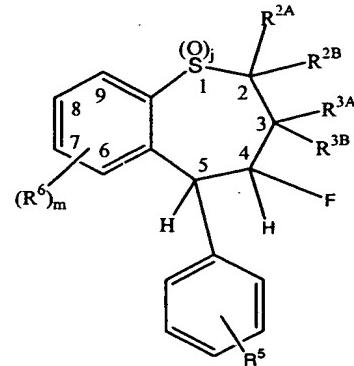
I-16

[68] herein R^{3A} and R^{3B} are independently selected from hydrogen and alkyl, wherein R^6 is the same as previously defined, and wherein R^5 is selected from the members (1) – (70) of Table 1 above. Note that while R^5 is described as being attached to the para-position of the phenyl ring, R^5 may be attached to either the ortho or the meta position of the subject phenyl ring described above (e.g., where appropriate, in any of Formulas I-9 to I-16 above and in any of Formulas I-17 to I-24 depicted below.). Preferably, the R^5 substituent is at the meta- or the para- position of the C_5 -phenyl group.

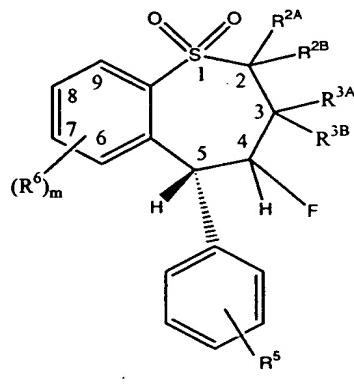
[69] Additional exemplary embodiments of ASBT inhibitors of the present invention are represented by formulas I-17 to I-24 below:



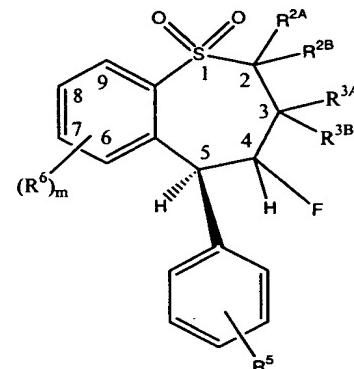
I-17



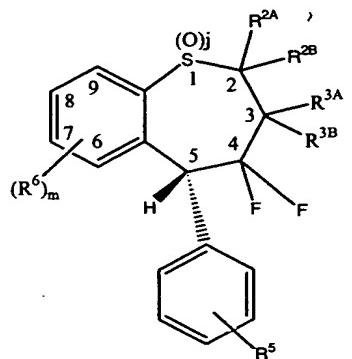
I-18



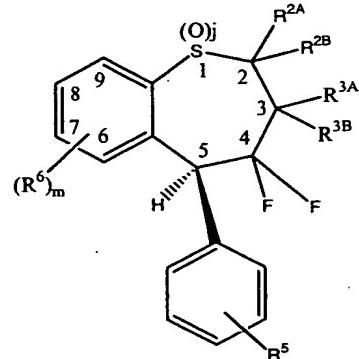
I-19



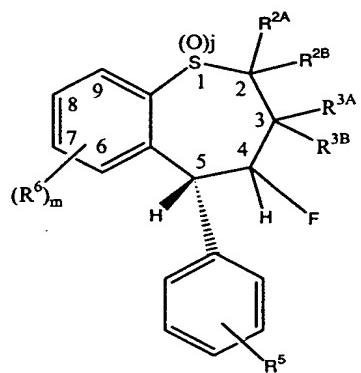
I-20



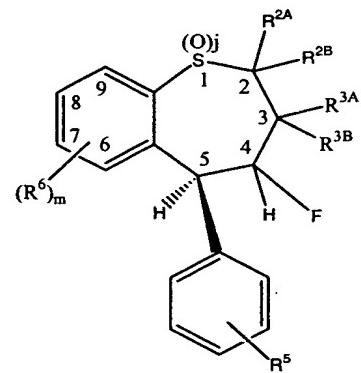
I-21



I-22



I-23



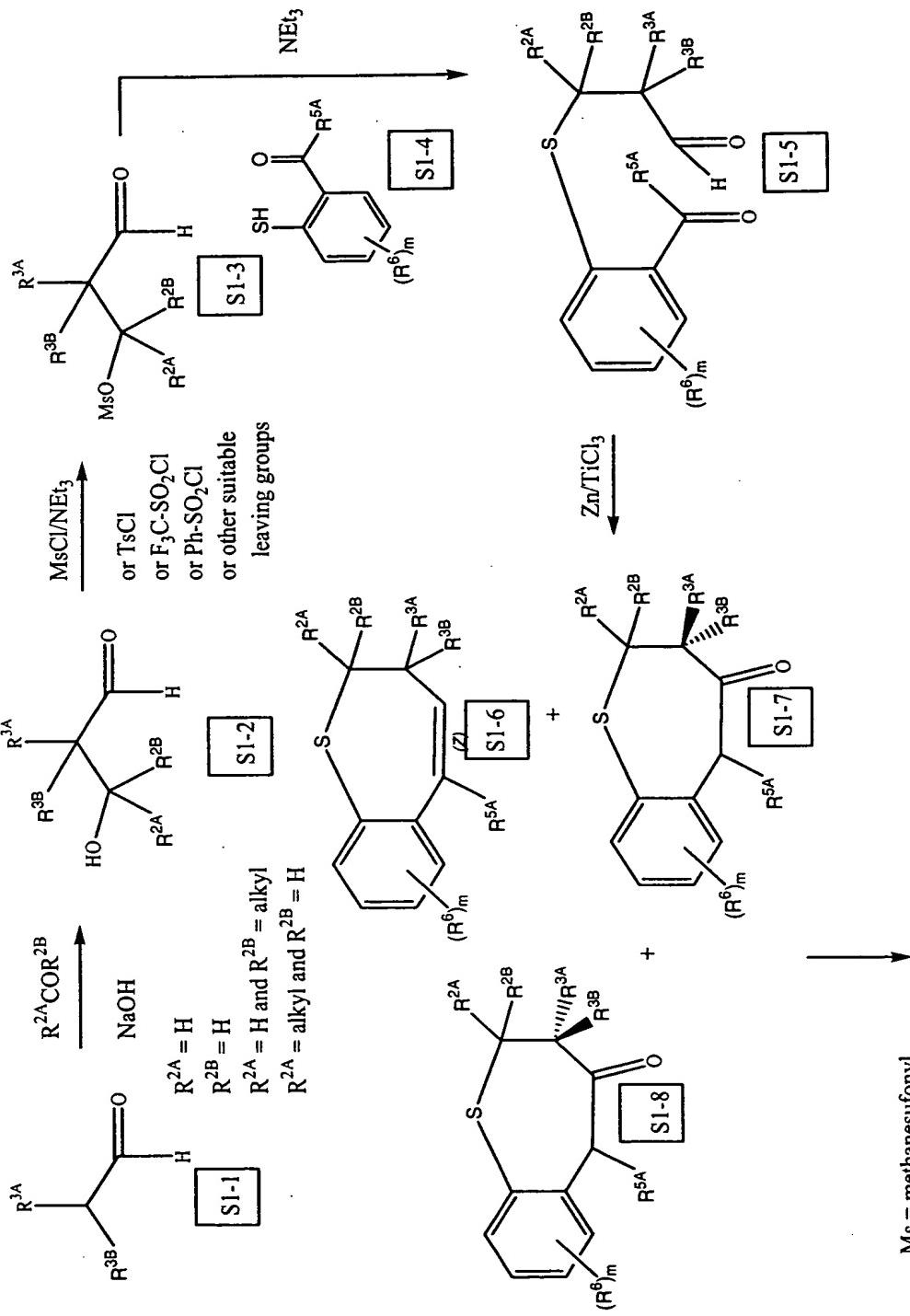
I-24

wherein R^{2A}, R^{2B}, R^{3A}, R^{3B}, R⁵, R⁶, m, and j are as previously described. Optionally, R^{2A} = R^{2B} = H and/or R^{3A} = R^{3B} and/or j = 2 and/or m = 1.

- [70] The novel fluorinated benzothiophene compounds of the present invention are safe and effective anti-hyperlipidemic agents. These compounds generally exhibit at least one desirable characteristic which includes, but is not limited to: (a) improved potency, (b) improved solubility profile, (c) improved compatibility with conventional routes of oral administration, (d) improved safety profile, and (e) elimination of a chiral center at the 4-position ring carbon in the case of the novel di-fluorinated benzothiophenes of the present invention.

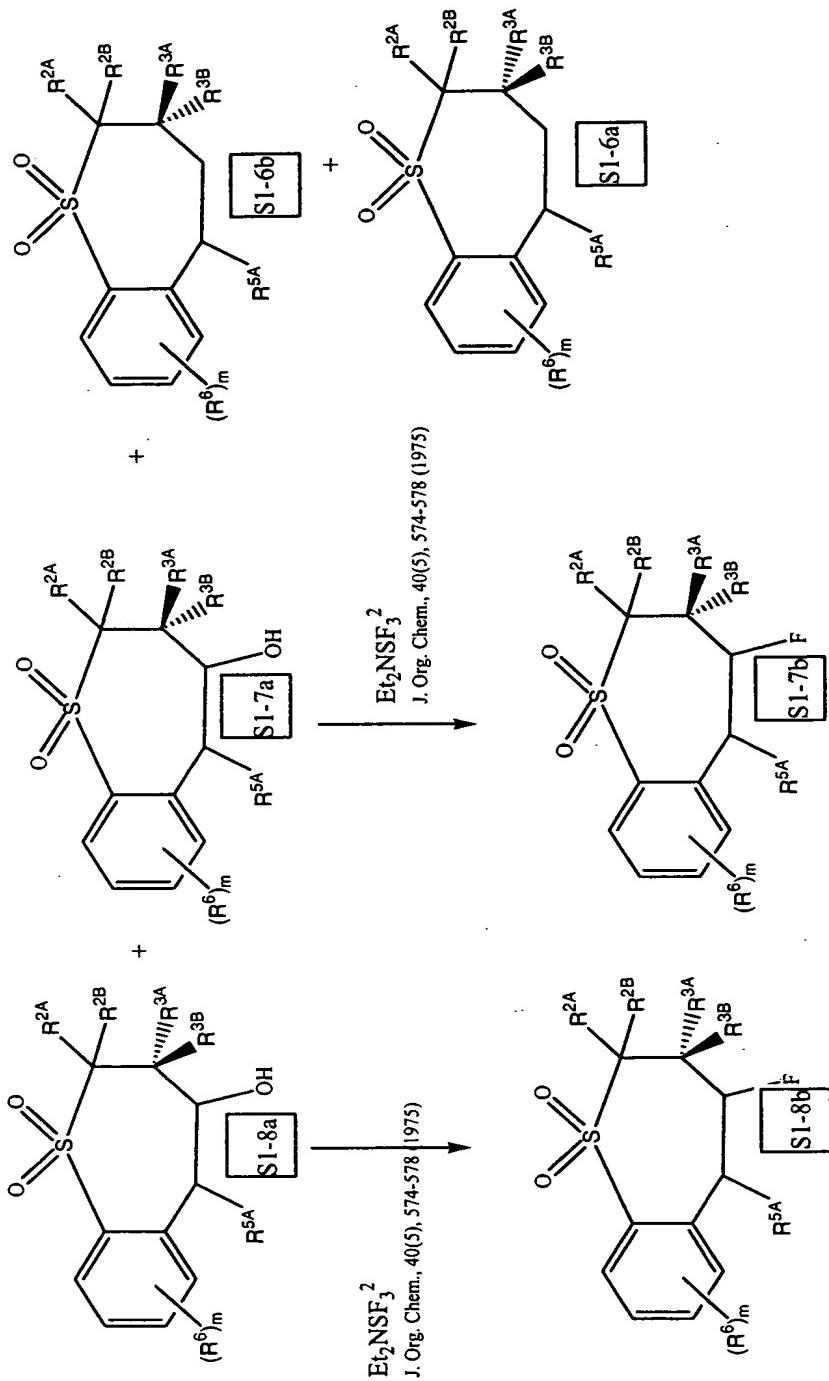
- [71] The compounds of the present invention are useful for, but not limited to, the treatment of one or more hyperlipidemic condition(s) including the prophylactic treatment of hyperlipidemia in a subject. The methods, compounds, pharmaceutical compositions and kits of the present invention also are useful for the prophylaxis and/or treatment of gallstones. Besides being useful for human treatment, the above-described compounds (*e.g.*, I-1 to I-24) also are useful for veterinary treatment of companion animals (*e.g.*, horses, dogs, cats, etc.), exotic animals and farm animals, including mammals, rodents, and the like. Even though the invention is described in terms of human biology, it will be understood by those of ordinary skill that the present invention is applicable to other mammals, as well.
- [72] The above-noted ASBT inhibitors of the present invention may be made according to the exemplary chemical Schemes 1 and 2 below:

SCHEME 1

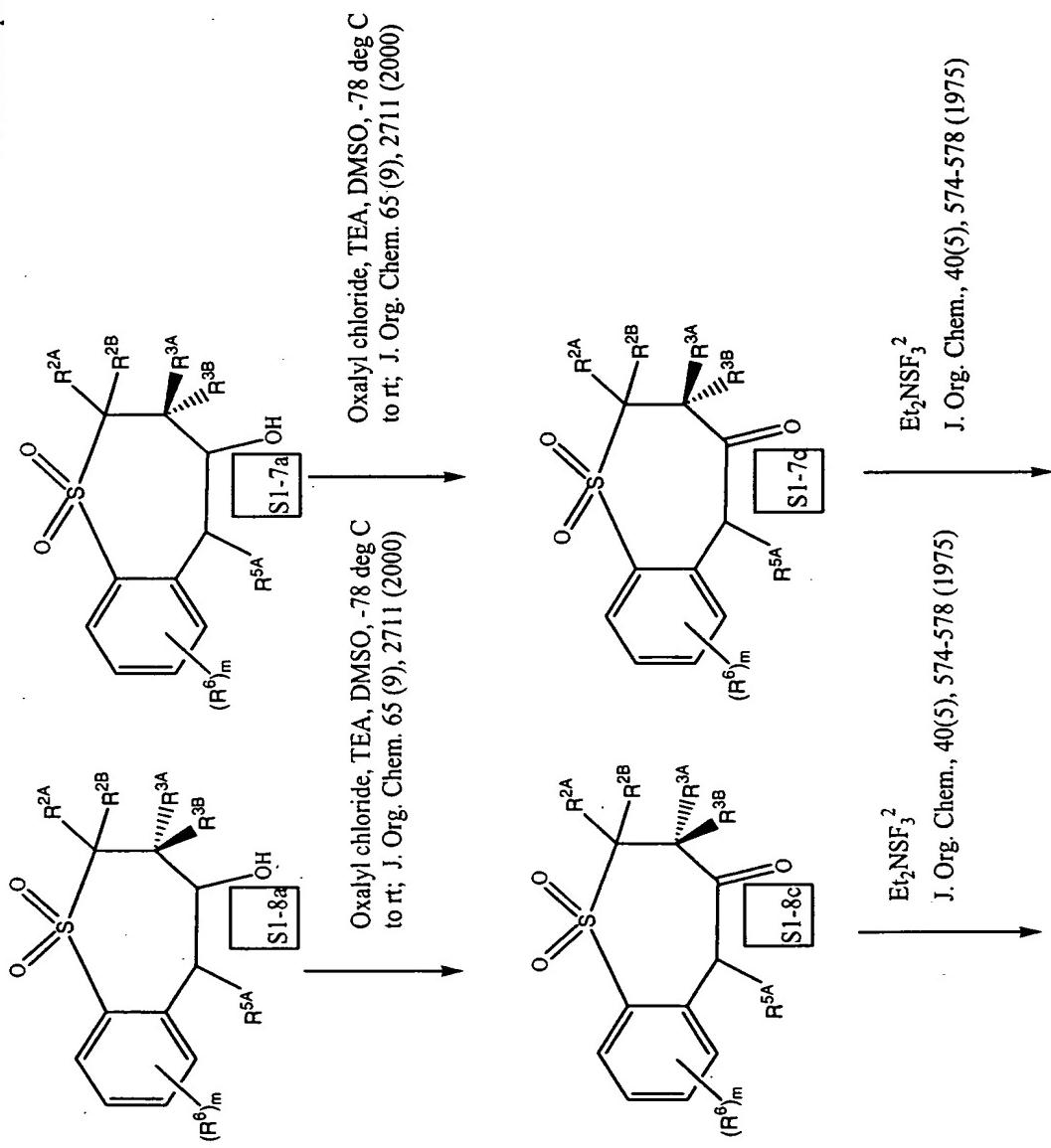


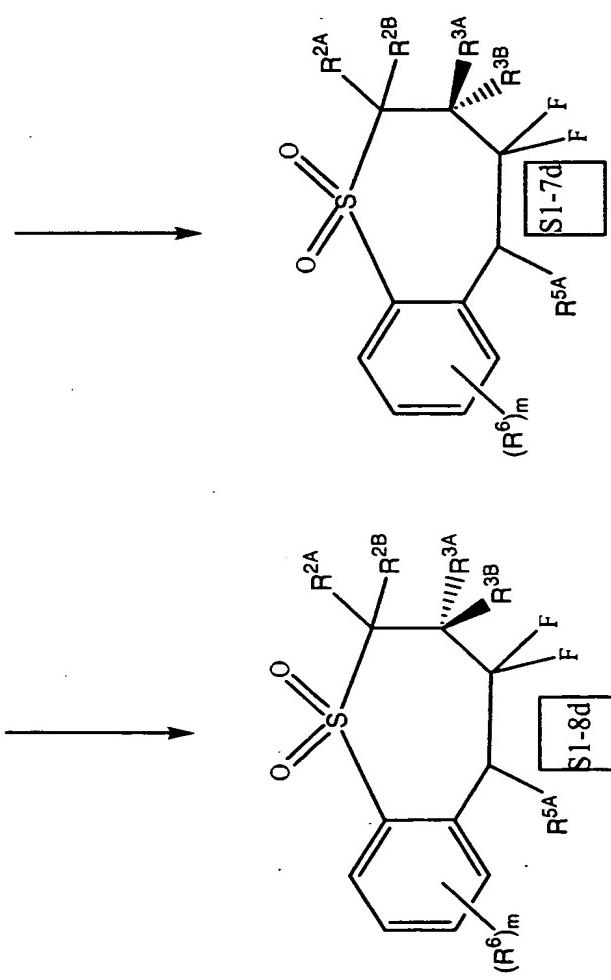
MCPBA = m-chloro-perbenzoic acid

1. x s MCPBA
2. H₂/Pd-C



rt = room temperature



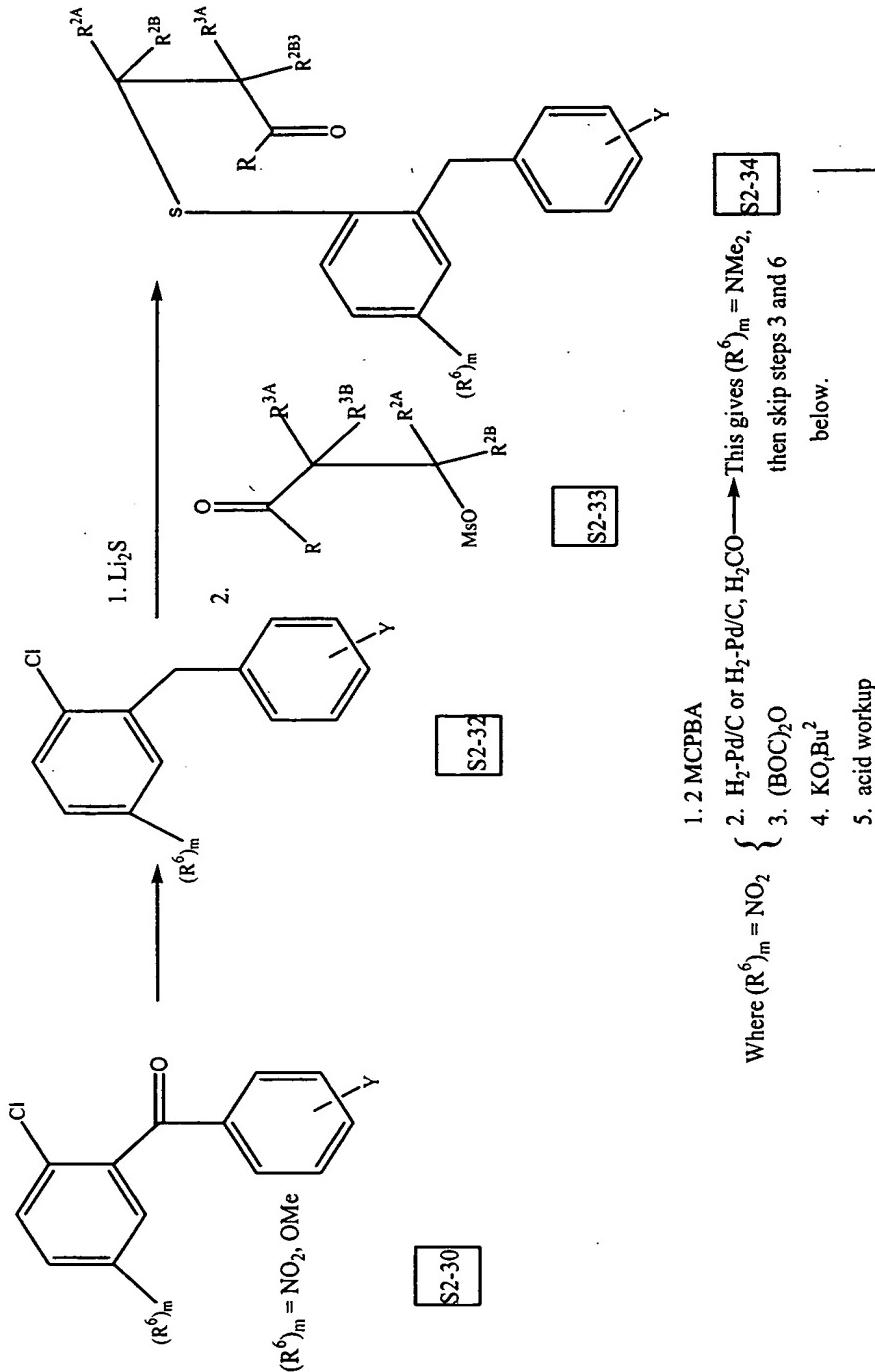


- [73] As indicated in Scheme 1, the aldehyde S1-1 is reacted with formaldehyde or an aldehyde and sodium hydroxide to yield the compound S1-2 which is converted to the mesylate S1-3 with methanesulfonyl chloride or other suitable leaving group and triethylamine as an exemplary solvent. See, for example, Chem. Ber. 98, 728-734 (1965). Reaction of the mesylate S1-3 with the thiophenol S1-4 in triethylamine yields the keto-aldehyde S1-5, which is prepared according to the procedure indicated in WO 93/16055. The keto-aldehyde S1-5 is then cyclized with a suitable cyclicizing agent such as Zn/TiCl₃ in refluxing ethylene glycol dimethyl ether (DME) to yield a racemic mixture of the ketone S1-7 and S1-8 (when R^{3A} ≠ R^{3B}) together with compound S1-6. Treatment of S1-7 and S1-8 with excess (e.g., 3 equivalents) of m-chloro-perbenzoic acid (MCPBA) yields the a sulfone epoxide (not shown) which, in turn, upon hydrogenation with palladium on carbon (H₂/Pd-C) as catalyst yields a racemic mixture of S1-7a and S1-8a (when R^{3A} ≠ R^{3B}) and another racemic mixture of S1-6a and S1-6b (when R^{3A} ≠ R^{3B}). It is noted that optically active compounds of the present invention can be prepared by using optically active starting materials of compound S1-2 or by resolution of compounds S1-7a and S1-8a. Resolution of compounds S1-7a and S1-8a can be accomplished with optical resolution agents well known in the art and described in J. Org. Chem., 39 (26), 3904-3906 (1974), J. Org. Chem., 42 (16), 2781-2782 (1977) and J. Org. Chem., 44 (26), 4891-4896 (1979).
- [74] Alcohols S1-7a and/or S1-8a can be converted to the mono-fluorinated compounds S1-7b and S1-8b by treatment with dimethylaminosulfur trifluoride (Et₂NSF₃²⁻) in accordance with the procedure outlined in J. Org. Chem., 40(5), 574-578 (1975) with retention of stereochemistry. In particular, the alcohol S1-7a and/or S1-8a is/are added to a solution of (Et₂NSF₃²⁻) in an inert solvent cooled to -50 to -78°C. The reaction mixture is then warmed to room temperature (or higher). Typically, an initial exothermic reaction may occur during the warm-up period. On occasion, a second exothermic reaction may also occur during the warm-up period. Lower boiling fluorides are distilled out of the reaction mixture at reduced pressure to yield compounds

S1-7b and/OR S1-8b. For the higher boiling fluorides, the reaction mixture should be mixed with water, the organic layer separated and dried, and any solvent should be removed from the separated organic layer by distillation. The product fluoride compounds can then be further purified by recyrstallization, or column chromatography.

- [75] To obtain the diflourinated compounds 7d and/or 8d, compounds S1-7a and/or S1-8a should first be converted to the ketones S1-7c and/or S1-8c by treatment with oxalyl chloride, triethanolamine (TEA) and dimethyl sulfoxide (DMSO) as indicated in J. Org. Chem., 65 (9), 2711-2715 (2000). Thereafter, ketones S1-7c and/or S1-8c can be converted to the difluorinated compounds S1-7d and/or S1-8d by the same procedure previously described for the conversion of S1-7a and S1-8a to S1-7b and S1-8b outlined in J. Org. Chem. 40(5), 574-578 (1975).
- [76] Also, optically active compounds S1-7d and S1-8d can be obtained by using optically active starting materials of compounds S1-2 or S1-3 or by using previously described optical resolving agents to separate optically active compounds S1-7a and S1-8a from each other. Thereafter, separated compounds S1-7a and S1-8a should be converted to S1-7c and S1-8c followed by conversion to S1-7d and S1-8d, respectively, as indicated above.

SCHEME 2

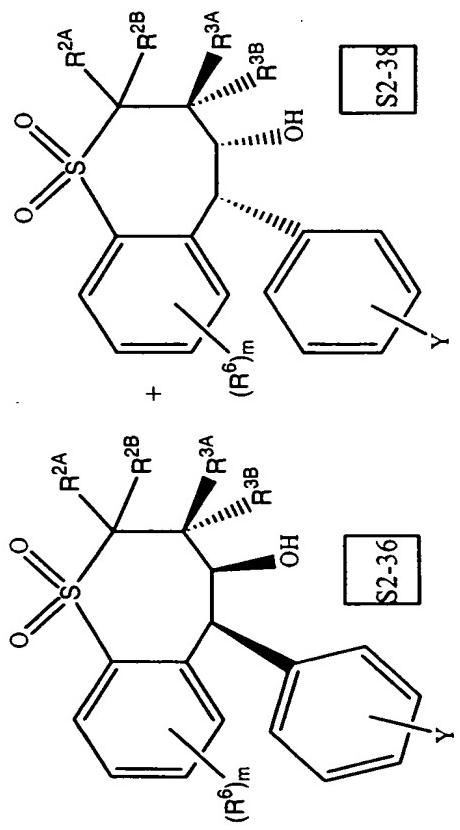


1. 2 MCPBA
Where $(R^\delta)_m = \text{NO}_2$ { 2. $\text{H}_2\text{-Pd/C}$ or $\text{H}_2\text{-Pd/C, H}_2\text{CO} \longrightarrow$ This gives $(R^\delta)_m = \text{NMe}_2$,
then skip steps 3 and 6

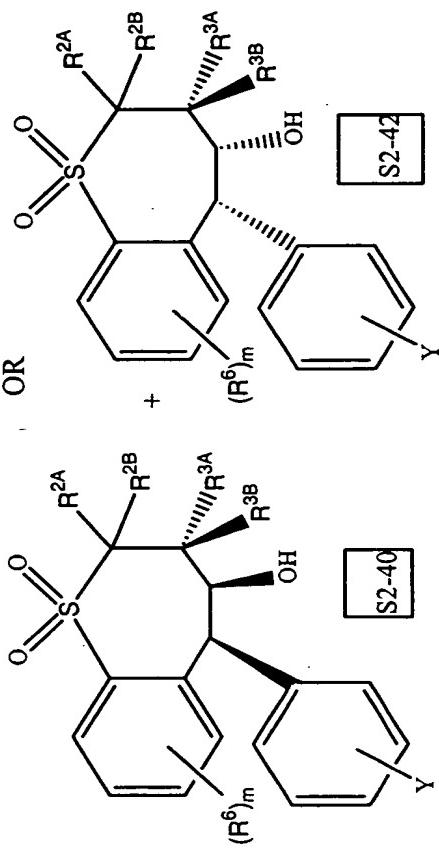
S2-34

below.

5. acid workup
6. Pd/C-H_2 , 100psi, 50 deg. C

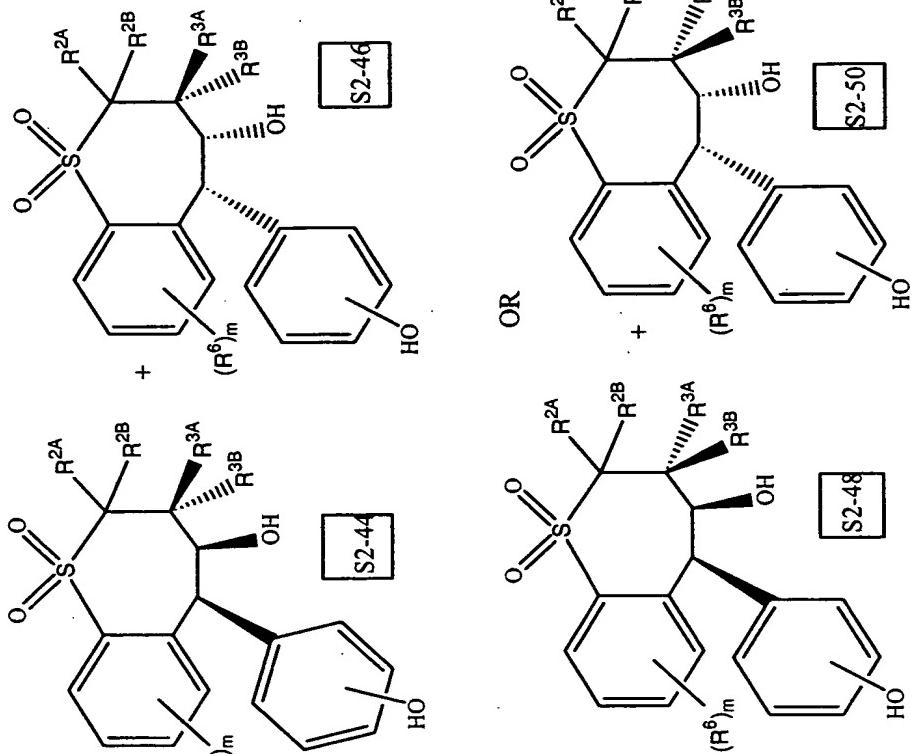
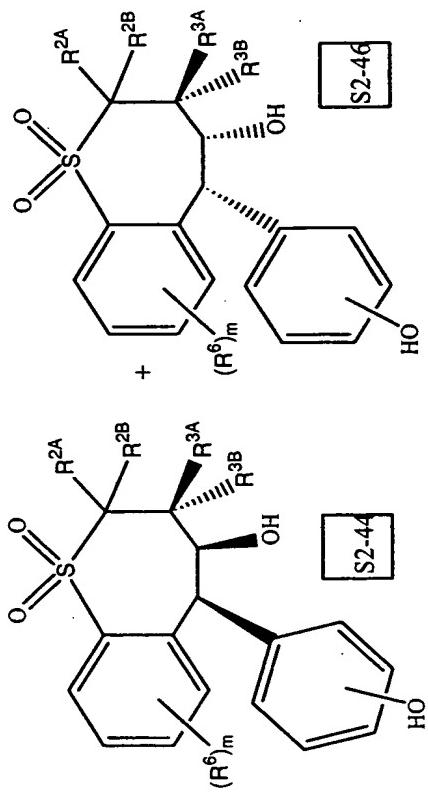


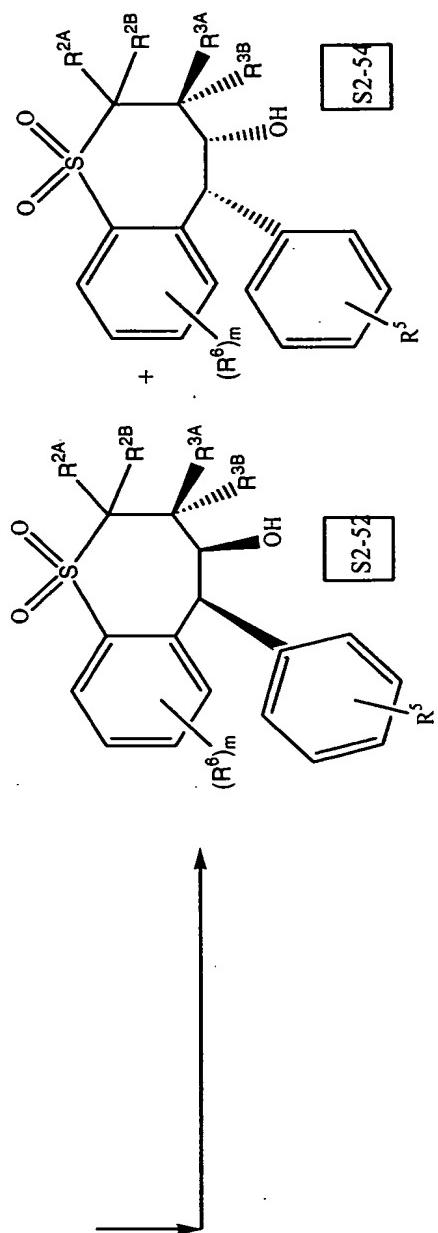
$(R^6)_m = \text{NH}_2, \text{OMe}, \text{NMe}_2$



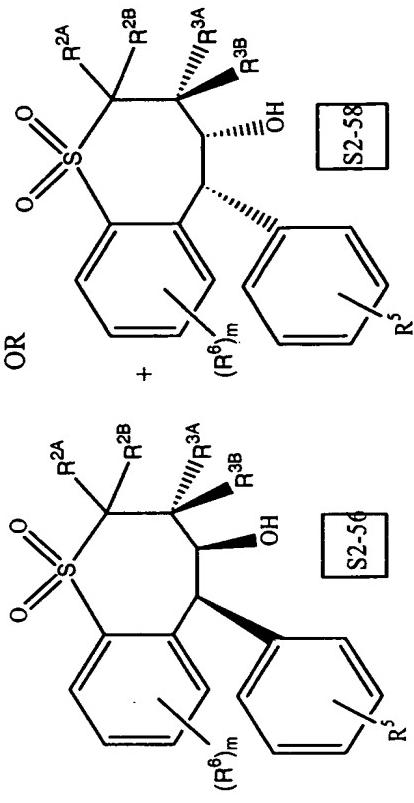


(where Y = MeO for each of 36, 38, 40 and 42)





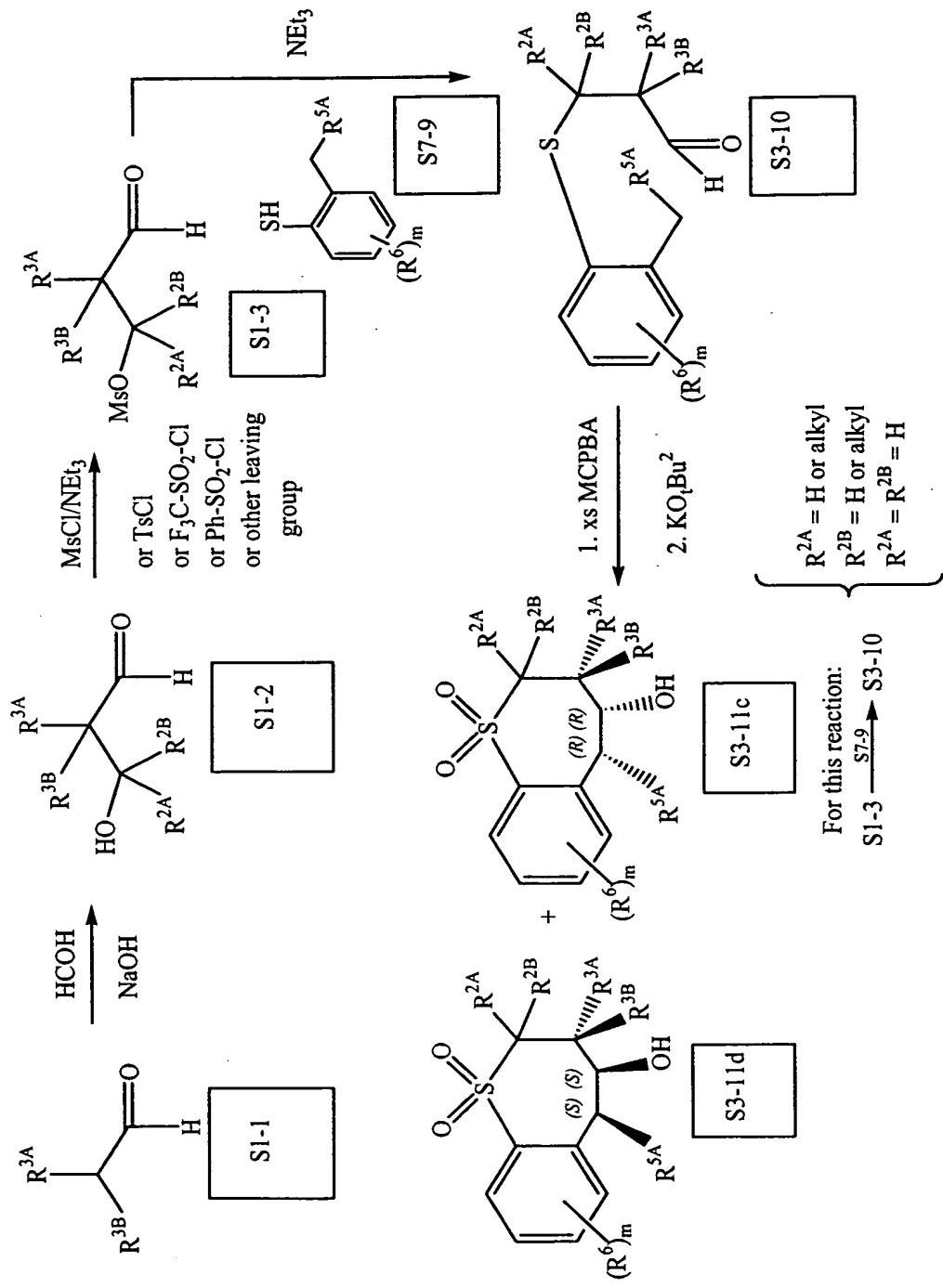
R^5 = substituents (1) - (70)
 noted in Table 1 for each of
 S2-52, S2-54, S2-56 and S2-58



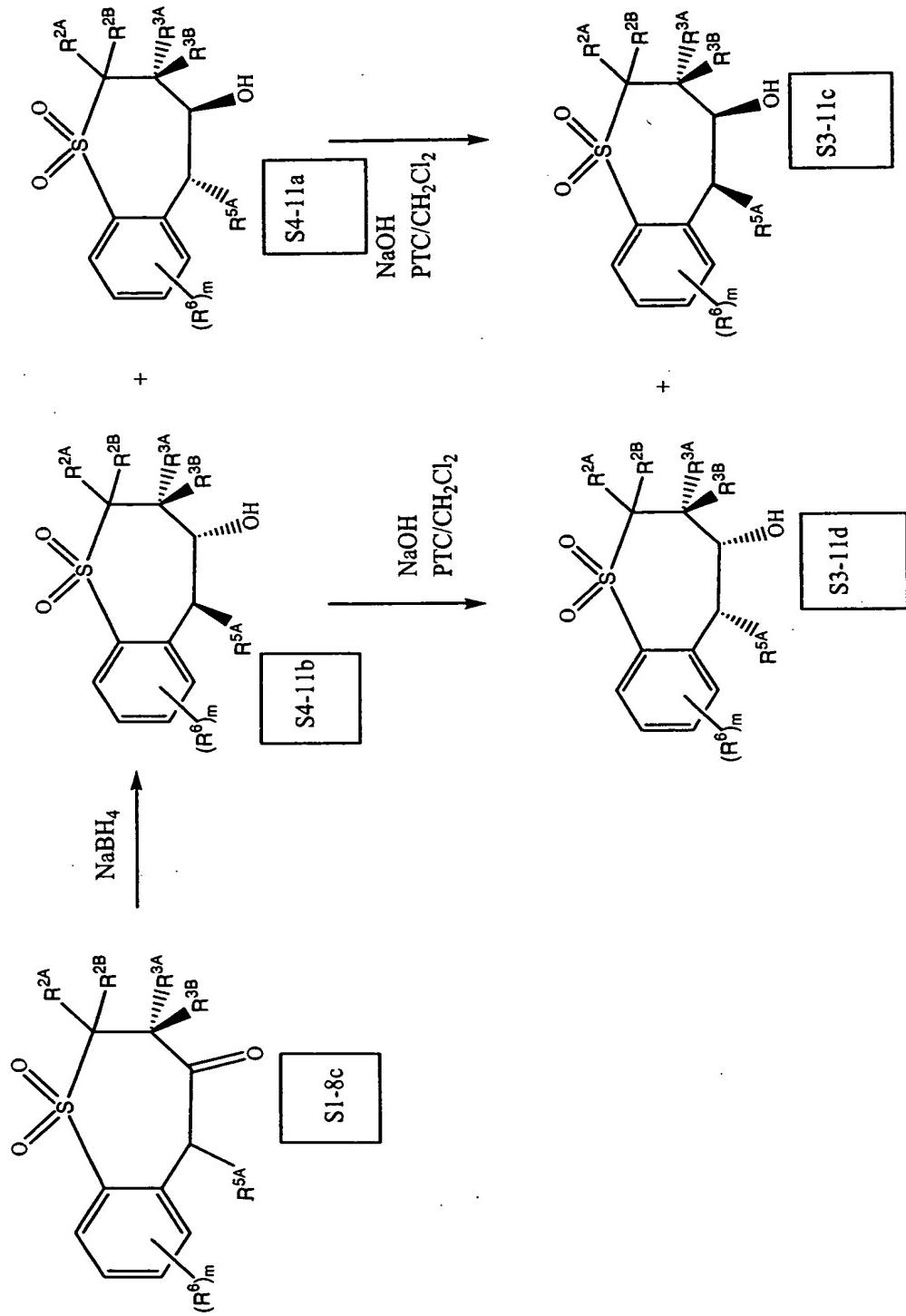
- [77] In Scheme 2, compound S2-30 is converted to compound S2-32 with triethylsilane and trifluoromethane sulfonic acid. Reaction of S2-32 with lithium sulfide followed by reacting the resulting sulfide with the mesylate S2-33 gives the sulfide S2-34. Oxidation of S2-34 with 2 equivalents of MCPBA, followed by reduction with H₂—Pd/C, protection of the resulting hydroxylamine with di-t-butylcarbonate, cyclization with potassium t-butoxide, removal of the t-butoxycarbonyl protecting groups (and acid workup) and hydrogenation with Pd/C—H₂ at 100 psi and 50 °C yields compounds S2-36, S2-38, S2-40 and S2-42 wherein, for example, R⁶ = -NH₂ and m = 1 (integer). In Scheme 2, compounds S2-36, S2-38, S2-40 and S2-42 are made using chiral starting materials of compound 33 or by resolving the chiral compounds S2-36, S2-38, S2-40 and S2-42 using the previously noted optical resolution agents. Further, in Scheme 2, Y typically is OMe. However, Y may be another alkoxy, or a halogen (F, Cl, Br, and I).
- [78] Exemplary conversion of 36, 38, 40 and 42 (e.g., wherein R⁶ = -NH₂ and m = 1 and Y = OMe) into 44, 46, 48 and 50 is accomplished according to the procedure outlined in Step 9 of Example 1401, *infra*. In particular, the methoxy compounds S2-36, S2-38, S2-40 and/or S2-42 (e.g., Y = OMe) and CH₃Cl are placed in a flask purged with N₂. The reaction mixture is then cooled to -78°C and boron tribromide (BBr₃) is added. The mixture is allowed to warm to room temperature. After about 4 hours, the reaction mixture is cooled to 0°C and then quenched with 10% K₂CO₃. Thereafter (about 10 min. later), the layers are separated and the aqueous layers extracted twice with ethyl ether. The CHCl₃ and ether extracts are combined, washed with saturated aqueous NaCl, dried (MgSO₄), filtered and concentrated *in vacuo* to yield the products S2-44, S2-46, S2-48 and /or S2-50.
- [79] Compounds S2-44, S2-46, S2-48 and S2-50 are then converted to compounds S2-52, S2-54, S2-56 and S2-58 (wherein R⁵ is a moiety selected from members (1) – (70) depicted in Table 1 above) according to the procedures for adding the same groups described and outlined in the Examples, *infra*.

- [80] After formation of compounds S2-52, S2-54, S2-56 and/or S2-58 (either formed with chiral starting materials or resolved using optical resolving agents), these compounds are subjected to the same mono-fluorinating procedures previously described and outlined in Scheme 1 for the conversion of S1-7a and S1-8a to S1-7b and S1-8b. By carrying out such steps, the corresponding mono-fluorinated compounds of S2-52, S2-54, S2-56 and/or S2-58 are formed, wherein a single C-F bond is formed at the C-4 carbon of the benzothiepine ring, exemplarily depicted in Formulas I-2 to I-8, Formulas I-11 to I-16, Formulas I-19 to I-20, and Formulas I-23 to I-24.
- [81] Similarly, the corresponding di-fluorinated compounds of the hydroxy compounds S2-52, S2-54, S2-56 and/or S2-58 are made by subjecting compounds S2-52, S2-54, S2-56 and/or S2-58 to the same di-fluorinating procedures previously described and outlined in Scheme 1 for the conversion of S1-7a and S1-8a to S1-7d and S1-8d. By so doing, the corresponding di-fluorinated compounds of the hydroxy compounds S2-52, S2-54, S2-56 and/or S2-58 are formed. Exemplary difluorinated compounds are depicted in Formulas I-1, I-9, I-10, I-17, and I-22.
- [82] Additional Schemes for forming compounds S3-11c and S3-11d analogous to compounds S1-7a and S1-8a are provided in Schemes 3 – 5 below. Scheme 6 below outlines the procedures for forming other compounds S6-15c and S6-15d analogous to compounds S3-11c and S3-11d, where the stereochemistry at the C-3 carbon is varied when $R^{3A} \neq R^{3B}$. Once formed, compounds S3-11c, S3-11d, S6-15c and S6-15d are subjected to the procedures previously described and outlined in Scheme 2 for the attachment of R^5 groups and then subjected to the procedures previously described and outlined in Scheme 1 for formation of the analogous mono-fluorinated and di-fluorinated compounds having the appropriate R^5 groups attached off of the phenyl ring attached to the C-5 carbon as depicted or indicated in connection with one or more of Formulas I-1 to I-24. Finally, Scheme 7 below outlines the procedure for forming compound S7-9 utilized in Scheme 3. Schemes 3-7 are as follows:

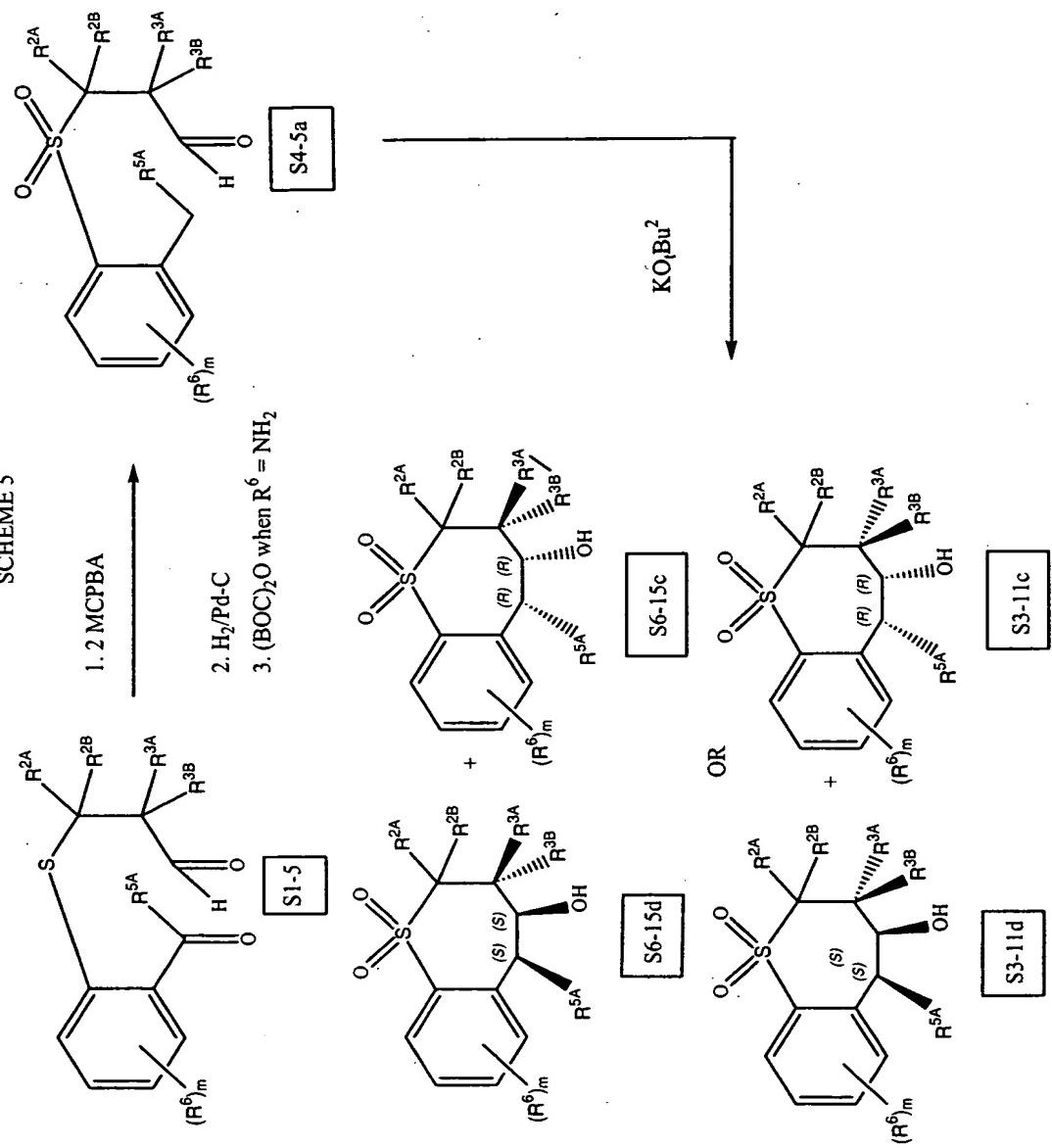
SCHEME 3

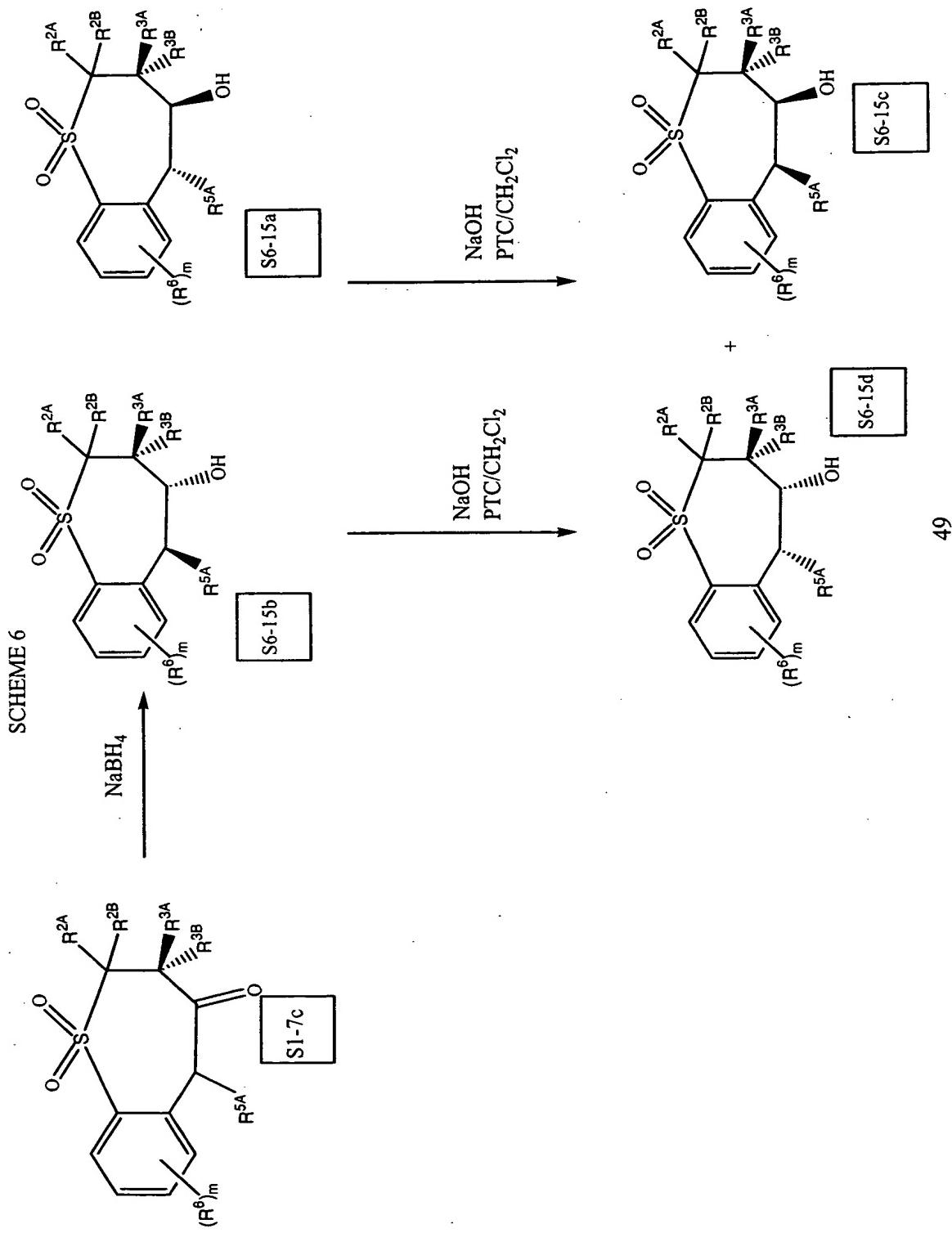


SCHEME 4

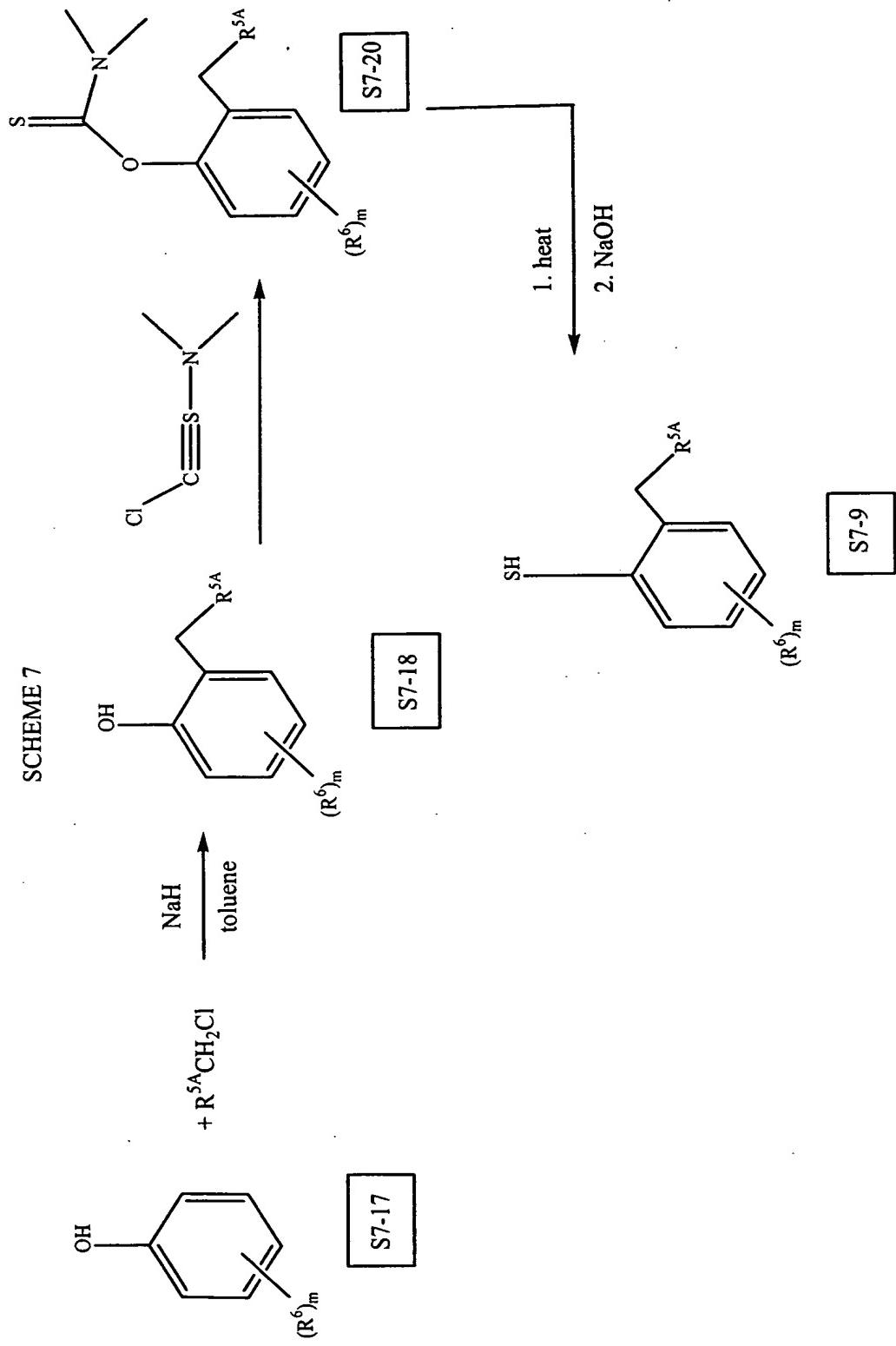


SCHEME 5





SCHEME 7



- [83] In Scheme 3, compound S1-3 is formed according to the same procedure outlined in Scheme 1. Thereafter, compound S1-3 is reacted with thiophenol S7-9 (*e.g.*, made according to Scheme 7, *infra*) to yield the sulfide-aldehyde S3-10. Oxidation of S3-10 with 2 equivalents of MCPBA and then cyclization with potassium t-butoxide yields compounds S3-11c and S3-11d. As noted with Scheme 1, either chiral starting materials (such as chiral starting compounds corresponding to those of S1-2) or optical resolving agents may be used to form compounds S3-11c and/or S3-11d.
- [84] In Scheme 4, compound 8c is reduced with NaBH₄ to yield compounds S4-11a and/or S4-11b (made with chiral starting materials or optical resolving agents). Both S4-11a and S4-11b depict the R^{S^A} group and the OH group on opposite sides. Compounds S4-11a and S4-11b can be converted to compounds S3-11c and S3-11d, respectively, by treating the former compounds (S4-11a and/or S4-11b) in methylene chloride with 40-50% sodium hydroxide in the presence of a phase transfer catalyst (PTC). The transformation of S4-11a and S4-11b to S3-11c and S3-11d, respectively, can also be carried out with potassium t-butoxide in tetahydrofuran (THF).
- [85] In Scheme 5, compound S1-5 is made according to the procedures described and outlined in Scheme 1. Compound S1-5 is oxidized with 2 equivalents of MCPBA and then treated with H₂—Pd/C when R⁶ = NO₂, and protect with (BOC)₂O to yield compound S4-5a. Compound S4-5a, in turn, is cyclized with potassium t-butoxide to yield compounds S3-11c, S3-11d, S6-15c and/or S6-15d (as earlier noted, S3-11c, S3-11d, S6-15c, and/or S6-15d are formed using chiral starting materials or with optical resolving agents).
- [86] In Scheme 6, compound S1-7c (formed according to Scheme 1) is reduced with sodium borohydride to give compounds S6-15a and/or S6-15b. Note that compounds S6-15a and S6-15b are formed by utilizing chiral starting materials or by using optical resolving agents. Thereafter, compounds S6-15a and S6-15b can be converted to compounds S6-15c and S6-15d, respectively, by reaction in methylene chloride with 40-50% sodium hydroxide in the

presence of a phase transfer agent (PTC) as previously described in connection with Scheme 4.

- [87] Scheme 7 outlines an exemplary process for forming compound S7-9 used in Scheme 1. In particular, compound S7-17 is alkylated with an arylmethyl chloride in a nonpolar solvent according to J. Chem. Soc., part 2, 2431-2432 (1958) which gives the ortho-substituted phenol S7-18. Phenol S7-18 is converted to the thiophenol S7-9 via thiocarbamate S7-20 by the procedure described in J. Org. Chem., 31, 3980-3984 (1966). The phenol S7-18 is first reacted with dimethyl thiocarbamoyl chloride and triethylamine to give the thiocarbamate 20 which is chemically rearranged at 200-300°C., and then the rearranged product is hydrolyzed with sodium hydroxide to yield the thiophenol S7-9. Alternatively, thiophenol S7-9 can also be obtained from an analogous 2-acylphenol (*i.e.*, analogous to S7-18 wherein the carbon to which R^{5A} is attached has a carbonyl oxygen attached to it as well — not shown) via the thiocarbamate intermediate S7-20 using ClC(S)N(CH₃)₂ as used before to convert S7-18 to S7-20.
- [88] Also, see Example 60 (Scheme 8), Example 1396 (Scheme 9), Example 1397 (Schemes 10 and 11). Further, various benzothiepene intermediates can be prepared according to U.S. Pat. No. 5,994,391 and WO 99/32478.
- [89] Additional embodiments of the claimed invention include compounds of formulas I-1 to I-24 wherein the substituents are as described below. For example,
- [90] (a) R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and alkyl;
- [91] (b) R^{3A} and R^{3B} are independently selected from the groups consisting of hydrogen; alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocyclyoxyalkyl;

heterocycloxyalkenyl; heterocyclyoxyalkynyl; alkylaryl; and (polyalkyl)aryl;
or

R^{3A} and R^{3B} taken together with the carbon to which they are attached form
 C_3-C_{10} cycloalkyl or C_3-C_{10} cycloalkenyl;

- [92] wherein the R^{3A} and R^{3B} alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocycloxyalkyl; heterocycloxyalkenyl; heterocycloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may be substituted with one or more radicals selected from the group consisting of -CN; halogen; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR⁹; -S⁺R⁹R¹⁰A⁻; -PR⁹R¹⁰; -P⁺R⁹R¹⁰R^wA⁻; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; and
- [93] wherein the R^{3A} and R^{3B} alkyl; cycloalkyl; alkenyl; cycloalkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; aryloxyalkyl; aryloxyalkenyl; aryloxyalkynyl; heterocycloxyalkyl; heterocycloxyalkenyl; heterocycloxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻-; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻-; -PR⁹-; -P(O)R⁹-; -P⁺R⁹R¹⁰A⁻-; or phenylene;
- [94] (c) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹; or R^{4A} and R^{4B} together form =O; =NOR⁹; =S; =NNR⁹R¹⁰; =NR⁹; or =CR¹¹R¹²;
- [95] (d) R^{5A} and R^5 are independently selected from the group consisting of alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

- [96] wherein the R^{5A} and R^5 alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radicals optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and
- [97] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5A} and R^5 radicals optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR¹⁹; -NR¹⁹R²⁰; -SR¹⁹; -S(O)R¹⁹; -SO₂R¹⁹; -SO₃R¹⁹; -CO₂R¹⁹; -CONR¹⁹R²⁰; -N⁺R⁹R¹⁹R²⁰A⁻; -P(O)R¹⁹R²⁰; -PR¹⁹R²⁰; -P⁺R⁹R¹⁹R²⁰A⁻; and -P(O)(OR¹⁹)OR²⁰; and
- [98] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5A} and R^5 radicals optionally may have one or more carbons replaced by -O-; -NR¹⁹-; -N⁺R¹⁹R²⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R¹⁹A⁻; -PR¹⁹-; -P(O)R¹⁹-; -P⁺R¹⁹R²⁰A⁻; or phenylene;

[99] (e) R^{5B} is selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$;

$-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$;

[100] wherein the R^{5B} alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radical optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; $-CN$; $-NO_2$; oxo; alkyl; polyalkyl; haloalkyl; hydroxyalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$; and

[101] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5B} radical optionally may be further substituted with one or more radicals selected from the group consisting of $-CN$; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; $-OR^{19}$; $-NR^{19}R^{20}$; $-SR^{19}$; $-S(O)R^{19}$; $-SO_2R^{19}$; $-SO_3R^{19}$; $-CO_2R^{19}$; $-CONR^{19}R^{20}$; $-N^+R^9R^{19}R^{20}A^-$; $-P(O)R^{19}R^{20}$; $-PR^{19}R^{20}$; $-P^+R^9R^{19}R^{20}A^-$; and $-P(O)(OR^{19})OR^{20}$; and

- [102] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5B} radical optionally may have one or more carbons replaced by -O-; $-NR^{19}-$; $-N^+R^{19}R^{20}A^-$; -S-; $-SO-$; $-SO_2-$; $-S^+R^{19}A^-$; $-PR^{19}-$; $-P(O)R^{19}-$; $-P^+R^{19}R^{20}A^-$; or phenylene;
- [103] (f) one or more R^6 (wherein $m = 1, 2, 3$, or 4 in $(R^6)^m$) are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-S(O)2R^{13}$; $-SO_3R^{13}$; $-S^+R^{13}R^{14}A^-$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; -OM; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-NR^{14}C(O)R^{13}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-OR^{18}$; $-S(O)_nNR^{13}R^{14}$; $-NR^{13}R^{18}$; $-NR^{18}OR^{14}$; $-N^+R^{13}R^{14}R^{15}A^-$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;
- [104] wherein the one or more R^6 alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; acyloxy radicals optionally may be further independently substituted with one or more radicals selected from the group consisting of halogen; -CN; oxo; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{11}R^{12}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue;
- [105] wherein the one or more R^6 quaternary heterocyclyl radical optionally may be independently substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl;

heterocyclalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -P(O)R¹³R¹⁴; -P¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; -N⁺R¹³R¹⁴R¹⁵A⁻; and carbohydrate residue;

- [106] wherein the one or more R⁶ radicals comprising carbon optionally may independently have one or more carbons replaced by -O-; -NR¹³-; -N⁺R¹³R¹⁴A⁻; -S-; -SO-; -SO₂-; -S⁺R¹³A⁻; -PR¹³-; -P(O)R¹³-; -PR¹³R¹⁴; -P⁺R¹³R¹⁴A⁻; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; or -P(O)R⁹; or
- [107] two R⁶ groups attached to adjacent carbon atoms (e.g., adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C₄-C₁₂ mono- or bi-cyclic carbocyclic or heterocyclic ring; a mono- or bi-cyclic carbocyclic or heterocyclic ring; or a mono- or bi-cyclic carbocyclic or heterocyclic ring;
- [108] wherein the mono- or bi-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; alkyl; haloalkyl; alkoxy; aryl; heterocyclyl; R^T; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹¹R¹²A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue;

- [109] (g) wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl;
- [110] (h) wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [111] (i) wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [112] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [113] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl;

aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

- [114] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and
- [115] (j) wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M; and
- [116] (k) wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl; and
- [117] wherein the R¹⁸ alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl radical optionally may be

substituted with one or more radicals selected from the group consisting of halogen; -CN; NO₂; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹¹R¹²A⁻; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; -CONR⁹R¹⁰; -SO₂OM; -SO₂NR⁹R¹⁰; -PR⁹R¹⁰; -P(OR¹³)OR¹⁴; -PO(OR¹⁶)OR¹⁷; and -C(O)OM; and

[118] (l) wherein R¹⁹ and R²⁰ are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and

[119] (m) wherein M is a pharmaceutically acceptable cation, wherein A⁻ is a pharmaceutically acceptable anion; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[120] According to another embodiment, the invention includes compounds of formulas I-1 to I-24 having the following substituents:

[121] (a1) R^{2A} and R^{2B} are independently selected from the group consisting of hydsrogen and alkyl;

[122] (b1) R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl; or

R^{3A} and R^{3B} taken together with the carbon to which they are attached form C₃-C₇ cycloalkyl or C₃-C₇ cycloalkenyl;

[123] wherein the R^{3A} and R^{3B} alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may be substituted with one or more radicals selected from the group consisting of -CN; halogen; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR⁹; -S⁺R⁹R¹⁰A⁻; -PR⁹R¹⁰; -P⁺R⁹R¹⁰R^wA⁻; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; and

- [124] wherein the R^{3A} and R^{3B} alkyl; cycloalkyl; alkenyl; alkynyl; arylalkyl; alkoxyalkyl; alkoxyalkenyl; alkoxyalkynyl; alkylaryl; and (polyalkyl)aryl radicals optionally may have one or more carbons replaced by -O-; $-NR^9-$; $-N^+R^9R^{10}A^-$; $-S-$; $-SO-$; $-SO_2-$; $-S^+R^9A^-$; $-PR^9-$; $-P(O)R^9-$; $-P^+R^9R^{10}A^-$, or phenylene;
- [125] (c1) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$; or R^{4A} and R^{4B} together form =O; =NOR⁹; =S; =NNR⁹R¹⁰; =NR⁹; or =CR¹¹R¹²;
- [126] (d1) R^{5A} is selected from the group consisting of alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$;
- [127] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^{5A} radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclyl; $-OR^{19}$; $-NR^{19}R^{20}$; $-SR^{19}$; $-S(O)R^{19}$; $-SO_2R^{19}$; $-SO_3R^{19}$; $-CO_2R^{19}$; $-CONR^{19}R^{20}$; $-N^+R^9R^{19}R^{20}A^-$; $-P(O)R^{19}R^{20}$; $-PR^{19}R^{20}$; $-P^+R^9R^{19}R^{20}A^-$; and $-P(O)(OR^{19})OR^{20}$; and
- [128] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^{5A} radical optionally

may have one or more carbons replaced by -O-; $-NR^{19}-$; $-N^+R^{19}R^{20}A^-$; -S-; -SO-; $-SO_2-$; $-S^+R^{19}A^-$; $-PR^{19}-$; $-P(O)R^{19}-$; $-P^+R^{19}R^{20}A^-$; or phenylene;

[129] (e1) R^{5B} is selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$;

[130] wherein the R^{5B} alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radical optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; -OM; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$; and

[131] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5B} radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; $-OR^{19}$; $-NR^{19}R^{20}$; $-SR^{19}$; $-S(O)R^{19}$; $-SO_2R^{19}$; $-SO_3R^{19}$; $-CO_2R^{19}$; $-CONR^{19}$

R^{20} ; $-N^+R^9R^{19}R^{20}A^-$; $-P(O)R^{19}R^{20}$; $-PR^{19}R^{20}$; $-P^+R^9R^{19}R^{20}A^-$; and $-P(O)(OR^{19})OR^{20}$; and

- [132] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5B} radical optionally may have one or more carbons replaced by $-O-$; $-NR^{19}-$; $-N^+R^{19}R^{20}A^-$; $-S-$; $-SO-$; $-SO_2-$; $-S^+R^{19}A^-$; $-PR^{19}-$; $-P(O)R^{19}-$; $-P^+R^{19}R^{20}A^-$; or phenylene;
- [133] (f1) one or more R^6 (wherein $m = 1, 2, 3$ or 4 in $(R^6)^m$) are independently selected from the group consisting of hydrogen; halogen; $-CN$; $-NO_2$; alkyl; cycloalkyl; polyalkyl; haloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; polyether; acyloxy; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-S(O)2R^{13}$; $-SO_3R^{13}$; $-S^+R^{13}R^{14}A^-$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-NR^{14}C(O)R^{13}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$;
 $-COR^{13}$; $-OR^{18}$; $-S(O)_nNR^{13}R^{14}$; $-NR^{13}R^{18}$; $-NR^{18}OR^{14}$; $-N^+R^{13}R^{14}R^{15}A^-$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; amino acid residue; peptide acid residue; polypeptide acid residue; and carbohydrate acid residue;
- [134] wherein the one or more R^6 alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; and acyloxy radicals optionally may be further independently substituted with one or more radicals selected from the group consisting of halogen; $-CN$; oxo; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^WA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-PR^9R^{10}$; $-P^+R^9R^{11}R^{12}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue;

- [135] wherein the one or more R⁶ quaternary heterocyclyl radical optionally may be independently substituted with one or more radicals selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; cycloalkyl; polyalkyl; haloalkyl; hydroxyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -P(O)R¹³R¹⁴; -PR¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and carbohydrate residue;
- [136] wherein the one or more R⁶ radicals comprising carbon optionally may independently have one or more carbons replaced by -O-; -NR¹³-; -N⁺R¹³R¹⁴A⁻; -S-; -SO-; -SO₂-; -S⁺R¹³A⁻; -PR¹³-; -P(O)R¹³-; -PR¹³-; -P⁺R¹³R¹⁴A⁻; phenylene; amino acid; peptide; polypeptide; carbohydrate; polyether; or polyalkyl; wherein said phenylene; amino acid; peptide; polypeptide; carbohydrate; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; or -P(O)R⁹-; or
- [137] two R⁶ groups attached to adjacent carbon atoms (*e.g.*, adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C₄-C₁₀ mono- or bi-cyclic carbocyclic or heterocyclic ring;
- [138] wherein the mono- or bi-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; alkyl; haloalkyl; alkoxy; aryl; heterocyclyl; R^T; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹¹R¹²A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue;

- [139] (g1) wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; carboxyaryl; carboxyheterocyclyl; amino; alkylamino; carboxyalkylamino; alkoxyalkylamino; and acyl;
- [140] (h1) wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; alkoxyalkyl; carboalkoxyalkyl; cycloalkyl; cycloalkenyl; haloalkyl; hydroxyalkyl; cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and
- [141] (i1) wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [142] R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [143] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [144] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl;

heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; haloalkyl; hydroxyalkyl; sulfoalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclalkyl; carboxy; carboxyalkyl; guanidinyl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and

- [145] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclalkyl; alkylarylalkyl; alkylheterocyclalkyl; alkylammoniumalkyl; aminoalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue; and
- [146] (j1) wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M; and
- [147] (k1) wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclalkoxycarbonyl; and

- [148] wherein the R¹⁸ alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxycarbonyl; arylalkoxycarbonyl; and heterocyclylalkoxycarbonyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; NO₂; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹¹R¹²A⁻; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; -CONR⁹R¹⁰; -SO₂OM; -SO₂NR⁹R¹⁰; -PR⁹R¹⁰; -P(OR¹³)OR¹⁴; -PO(OR¹⁶)OR¹⁷; and -C(O)OM; and
- [149] (11) wherein R¹⁹ and R²⁰ are independently selected from the group consisting of hydrogen; alkyl, alkenyl; alkynyl; aryl; and heterocyclyl; and
- [150] (m1) same as (m) above.
- [151] According to another embodiment the compounds of formulas I-1 to I-24 have the following substituents:
- [152] (a2) R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and (C₁-C₇)alkyl;
- [153] (b2) R^{3A} and R^{3B} taken together with the carbon to which they are attached form (C₃-C₇)cycloalkyl;
- [154] wherein the R^{3A} and R^{3B} (C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl(C₁-C₁₀)alkyl; (C₁-C₁₀)alkoxy(C₁-C₁₀)alkyl; (C₁-C₁₀)alkoxy(C₂-C₁₀)alkenyl; (C₁-C₁₀)alkoxy(C₂-C₁₀)alkynyl; (C₁-C₁₀)alkylaryl; and (polyalkyl)aryl radicals optionally may be independently substituted with one or more radicals selected from the group consisting of -CN; halogen; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^WA⁻; -SR⁹; -S⁺R⁹R¹⁰A⁻; -PR⁹R¹⁰; -P⁺R⁹R¹⁰R^WA⁻; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰;
- [155] wherein the R^{3A} and R^{3B} (C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl(C₁-C₁₀)alkyl; (C₁-C₁₀)alkoxy(C₁-C₁₀)alkyl; (C₁-

$C_{10})$ alkoxy(C_2-C_{10})alkenyl; (C_1-C_{10})alkoxy(C_2-C_{10})alkynyl; (C_1-C_{10})alkylaryl; and (polyalkyl)aryl radicals optionally may have one or more carbons independently replaced by -O-; $-NR^9-$; $-N^+R^9R^{10}A^-$; -S-; $-SO-$; $-SO_2-$; $-S^+R^9A^-$; $-PR^9$; $-P(O)R^9-$; $-P^+R^9R^{10}A^-$; or phenylene;

- [156] (c2) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen; (C_1-C_{10})alkyl; (C_2-C_{10})alkenyl; (C_2-C_{10})alkynyl; aryl; heterocyclyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$; or
- [157] R^{4A} and R^{4B} together form =O; =NOR⁹; =S; =NNR⁹R¹⁰; =NR⁹; or =CR¹¹R¹²; or
- [158] (d2) R^{5A} is selected from the group consisting of (C_1-C_{10})alkyl; (C_3-C_{10})cycloalkyl; (C_2-C_{10})alkenyl; (C_2-C_{10})alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; $-OR^9$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; and $-SO_3R^9$;
- [159] wherein the R^{5A} (C_1-C_{10})alkyl; (C_3-C_{10})cycloalkyl; (C_2-C_{10})alkenyl; (C_2-C_{10})alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radical optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; (C_1-C_{10})alkyl; polyalkyl; halo(C_1-C_{10})alkyl; (C_3-C_{10})cycloalkyl; (C_2-C_{10})alkenyl; (C_2-C_{10})alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C_1-C_{10})alkyl; heterocyclyl(C_1-C_{10})alkyl; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; -OM; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-P(O)R^{13}R^{14}$; $-PR^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$; and

- [160] wherein the (C_1 - C_{10})alkyl, polyalkyl, halo(C_1 - C_{10})alkyl, hydroxy(C_1 - C_{10})alkyl, (C_3 - C_{10})cycloalkyl, (C_2 - C_{10})alkenyl, (C_2 - C_{10})alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, aryl(C_1 - C_{10})alkyl, heterocyclyl(C_1 - C_{10})alkyl, and polyether substituents of the R^{5A} radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; (C_1 - C_{10})alkyl; (C_3 - C_{10})cycloalkyl; (C_2 - C_{10})alkenyl; (C_2 - C_{10})alkynyl; aryl; heterocyclyl; aryl(C_1 - C_{10})alkyl; heterocyclyl(C_1 - C_{10})alkyl; quaternary heterocyclyl; -OR¹⁹; -NR¹⁹R²⁰; -SR¹⁹; -S(O)R¹⁹; -SO₂R¹⁹; -SO₃R¹⁹; -CO₂R¹⁹; -CONR¹⁹R²⁰; -N⁺R⁹R¹⁹R²⁰A⁻; -P(O)R¹⁹R²⁰; -PR¹⁹R²⁰; -P⁺R⁹R¹⁹R²⁰A⁻; and -P(O)(OR¹⁹)OR²⁰; and
- [161] wherein the (C_1 - C_{10})alkyl, polyalkyl, halo(C_1 - C_{10})alkyl, hydroxy(C_1 - C_{10})alkyl, (C_3 - C_{10})cycloalkyl, (C_2 - C_{10})alkenyl, (C_2 - C_{10})alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, aryl(C_1 - C_{10})alkyl, heterocyclyl(C_1 - C_{10})alkyl, and polyether substituents of the R^{5A} radical optionally may have one or more carbons replaced by -O-; -NR¹⁹-; -N⁺R¹⁹R²⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R¹⁹A⁻; -PR¹⁹-; -P(O)R¹⁹-; -P⁺R¹⁹R²⁰A⁻; or phenylene;
- [162] (e2) R^{5B} is selected from the group consisting of hydrogen; (C_1 - C_{10})alkyl; (C_3 - C_{10})cycloalkyl; (C_2 - C_{10})alkenyl; (C_2 - C_{10})alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;
- [163] wherein the R^{5B} (C_1 - C_{10})alkyl; (C_3 - C_{10})cycloalkyl; (C_2 - C_{10})alkenyl; (C_2 - C_{10})alkynyl; aryl; heterocyclyl; and quaternary heterocyclyl radical optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; (C_1 - C_{10})alkyl; polyalkyl; halo(C_1 - C_{10})alkyl; (C_3 - C_{10})cycloalkyl; (C_2 - C_{10})alkenyl; (C_2 - C_{10})alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C_1 - C_{10})alkyl; heterocyclyl(C_1 - C_{10})alkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R

13 ; -NR 13 OR 14 ; -NR 13 NR 14 R 15 ; -CO₂R 13 ; -OM; -SO₂OM; -SO₂NR 13 R 14 ; -C(O)NR 13 R 14 ; -C(O)OM; -COR 13 ; -NR 13 C(O)R 14 ; -NR 13 C(O)NR 14 R 15 ; -NR 13 CO₂R 14 ; -OC(O)R 13 ; -OC(O)NR 13 R 14 ; -NR 13 SOR 14 ; -NR 13 SO₂R 14 ; -NR 13 SONR 14 R 15 ; -NR 13 SO₂NR 14 R 15 ; -P(O)R 13 R 14 ; -PR 13 R 14 ; -P $^+$ R 13 R 14 R 15 A $^-$; -P(OR 13)OR 14 ; -S $^+$ R 13 R 14 A $^-$; and -N $^+$ R 13 R 14 R 15 A $^-$;

- [164] wherein the (C₁-C₁₀)alkyl, polyalkyl, halo(C₁-C₁₀)alkyl, hydroxy(C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, aryl(C₁-C₁₀)alkyl, heterocyclyl(C₁-C₁₀)alkyl, and polyether substituents of the R^{5B} radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; (C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl; heterocyclyl; aryl(C₁-C₁₀)alkyl; heterocyclyl(C₁-C₁₀)alkyl; quaternary heterocyclyl; -OR 19 ; -NR 19 R 20 ; -SR 19 ; -S(O)R 19 ; -SO₂R 19 ; -SO₃R 19 ; -CO₂R 19 ; -CONR 19 R 20 ; -N $^+$ R 9 R 19 R 20 A $^-$; -P(O)R 19 R 20 ; -PR 19 R 20 ; -P $^+$ R 9 R 19 R 20 A $^-$; and -P(O)(OR 19)OR 20 ;
- [165] wherein the (C₁-C₁₀)alkyl, polyalkyl, halo(C₁-C₁₀)alkyl, hydroxy(C₁-C₁₀)alkyl, (C₃-C₁₀)cycloalkyl, (C₂-C₁₀)alkenyl, (C₂-C₁₀)alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, aryl(C₁-C₁₀)alkyl, heterocyclyl(C₁-C₁₀)alkyl, and polyether substituents of the R^{5B} radical optionally may have one or more carbons replaced by -O-; -NR 19 -; -N $^+$ R 19 R 20 A $^-$; -S-; -SO-; -SO₂-; -S $^+$ R 19 A $^-$; -PR 19 -; -P(O)R 19 -; -P $^+$ R 19 R 20 A $^-$; or phenylene;
- [166] (f2) one or more R⁶ (wherein m = 1, 2, 3 or 4 in (R⁶)m) radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; (C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; polyalkyl; halo(C₁-C₁₀)alkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C₁-C₁₀)alkyl; polyether; acyloxy; -OR 13 ; -NR 13 R 14 ; -SR 13 ; -S(O)R 13 ; -

S(O)2R^{13} ; $-\text{SO}_3\text{R}^{13}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; $-\text{NR}^{13}\text{OR}^{14}$; $-\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$; $-\text{CO}_2\text{R}^{13}$; $-\text{OM}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{NR}^{14}\text{C(O)R}^{13}$; $-\text{C(O)NR}^{13}\text{R}^{14}$; $-\text{C(O)OM}$; $-\text{COR}^{13}$; $-\text{OR}^{18}$; $-\text{S(O)nNR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{R}^{18}$; $-\text{NR}^{18}\text{OR}^{14}$; $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P(O)R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; amino acid residue; peptide acid residue; polypeptide acid residue; and carbohydrate acid residue;

- [167] wherein one or more of the R^6 ($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_3\text{-C}_{10}$)cycloalkyl; polyalkyl; halo($\text{C}_1\text{-C}_{10}$)alkyl; hydroxy($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_2\text{-C}_{10}$)alkenyl; ($\text{C}_2\text{-C}_{10}$)alkynyl; aryl; heterocyclyl; aryl($\text{C}_1\text{-C}_{10}$)alkyl; heterocyclyl($\text{C}_1\text{-C}_{10}$)alkyl; polyether; and acyloxy radicals optionally may be further independently substituted with halogen; $-\text{CN}$; oxo; $-\text{OR}^{16}$; $-\text{NR}^9\text{R}^{10}$; $-\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; $-\text{SR}^{16}$; $-\text{S(O)R}^9$; $-\text{SO}_2\text{R}^9$; $-\text{SO}_3\text{R}^{16}$; $-\text{CO}_2\text{R}^{16}$; $-\text{CONR}^9\text{R}^{10}$; $-\text{SO}_2\text{NR}^9\text{R}^{10}$; $-\text{PO}(\text{OR}^{16})\text{OR}^{17}$; $-\text{PR}^9\text{R}^{10}$; $-\text{P}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; or $-\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$;
- [168] wherein one or more of the R^6 quaternary heterocyclyl radical optionally may be independently substituted with one or more radicals selected from the group consisting of halogen; $-\text{CN}$; $-\text{NO}_2$; oxo; ($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_3\text{-C}_{10}$)cycloalkyl; polyalkyl; halo($\text{C}_1\text{-C}_{10}$)alkyl; hydroxy($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_2\text{-C}_{10}$)alkenyl; ($\text{C}_2\text{-C}_{10}$)alkynyl; aryl; heterocyclyl; aryl($\text{C}_1\text{-C}_{10}$)alkyl; heterocyclyl($\text{C}_1\text{-C}_{10}$)alkyl; polyether; $-\text{OR}^{13}$; $-\text{NR}^{13}\text{R}^{14}$; $-\text{SR}^{13}$; $-\text{S(O)R}^{13}$; $-\text{SO}_2\text{R}^{13}$; $-\text{SO}_3\text{R}^{13}$; $-\text{NR}^{13}\text{OR}^{14}$; $-\text{NR}^{13}\text{NR}^{14}\text{R}^{15}$; $-\text{CO}_2\text{R}^{13}$; $-\text{OM}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^{13}\text{R}^{14}$; $-\text{C(O)NR}^{13}\text{R}^{14}$; $-\text{C(O)OM}$; $-\text{COR}^{13}$; $-\text{P(O)R}^{13}\text{R}^{14}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; and $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; and
- [169] wherein one or more of the R^6 radicals comprising carbon optionally may independently have one or more carbons replaced by $-\text{O}-$; $-\text{NR}^{13}-$; $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; $-\text{S}-$; $-\text{SO}-$; $-\text{SO}_2-$; $-\text{S}^+\text{R}^{13}\text{A}^-$; $-\text{PR}^{13}-$; $-\text{P(O)R}^{13}-$; $-\text{PR}^{13}-$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{A}^-$

$^{14}\text{A}^-$; phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; polyether; or polyalkyl; wherein said phenylene; amino acid residue; peptide residue; polypeptide residue; carbohydrate residue; and polyalkyl optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; or -P(O)R⁹-; or

- [170] two R⁶ groups attached to adjacent carbon atoms (e.g., adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C₄-C₁₀ mono- or bi-cyclic carbocyclic or heterocyclic ring;
- [171] wherein the mono- or bi-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; (C₁-C₁₀)alkyl; halo(C₁-C₁₀)alkyl; (C₁-C₁₀)alkoxy; aryl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^WA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -P⁹R¹⁰; -P⁺R⁹R¹¹R¹²A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue;
- [172] (g2) wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of hydrogen; (C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl; heterocyclyl; ammonium(C₁-C₁₀)alkyl; (C₁-C₁₀)alkylammonium(C₁-C₁₀)alkyl; aryl(C₁-C₁₀)alkyl; heterocyclyl(C₁-C₁₀)alkyl; carboxy(C₁-C₁₀)alkyl; carbo(C₁-C₁₀)alkoxy(C₁-C₁₀)alkyl; carboxyheterocyclyl; carboxy(C₁-C₁₀)alkylamino; and acyl; and
- [173] (h2) wherein R¹¹ and R¹² are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; (C₁-C₁₀)alkyl; (C₂-C₁₀)alkenyl; (C₂-C₁₀)alkynyl; aryl; heterocyclyl; aryl(C₁-C₁₀)alkyl; carboxy(C₁-C₁₀)alkyl; carbo(C₁-C₁₀)alkoxy(C₁-C₁₀)alkyl; (C₃-C₁₀)cycloalkyl; cyano(C₁-C₁₀)alkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R

R^{10} ; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring;

- [174] (i2) wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; (C_1-C_{10}) alkyl; halo(C_1-C_{10})alkyl; (C_3-C_{10}) cycloalkyl; polyalkyl; (C_2-C_{10}) alkenyl; (C_2-C_{10}) alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C_1-C_{10})alkyl; heterocyclyl(C_1-C_{10})alkyl; quaternary heterocyclyl(C_1-C_{10})alkyl; (C_1-C_{10})alkylaryl(C_1-C_{10})alkyl; (C_1-C_{10})alkylheterocyclyl(C_1-C_{10})alkyl; (C_1-C_{10})alkylammonium(C_1-C_{10})alkyl; carboxy(C_1-C_{10})alkylaminocarbonyl(C_1-C_{10})alkyl; and polyether; or
- [175] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [176] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [177] wherein the R^{13} , R^{14} , and R^{15} (C_1-C_{10})alkyl; halo(C_1-C_{10})alkyl; (C_3-C_{10}) cycloalkyl; polyalkyl; (C_2-C_{10}) alkenyl; (C_2-C_{10}) alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl(C_1-C_{10})alkyl; heterocyclyl(C_1-C_{10})alkyl; quaternary heterocyclyl(C_1-C_{10})alkyl; (C_1-C_{10})alkylaryl (C_1-C_{10})alkyl; (C_1-C_{10})alkylheterocyclyl(C_1-C_{10})alkyl; (C_1-C_{10})alkylammonium(C_1-C_{10})alkyl; aminocarbonyl(C_1-C_{10})alkyl; (C_1-C_{10})alkylaminocarbonyl(C_1-C_{10})alkyl; carboxy(C_1-C_{10})alkylaminocarbonyl(C_1-C_{10})alkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; (C_1-C_{10})alkyl; sulfo(C_1-C_{10})alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl(C_1-C_{10})alkyl; carboxy; carboxy(C_1-C_{10})alkyl; guanidinyl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -

SO_3R^{16} ; $-\text{CO}_2\text{R}^{16}$; $-\text{CONR}^9\text{R}^{10}$; $-\text{SO}_2\text{NR}^9\text{R}^{10}$; $-\text{PO}(\text{OR}^{16})\text{OR}^{17}$; $-\text{PR}^9\text{R}^{10}$; $-\text{P}^+\text{R}^9\text{R}^{10}\text{R}^{11}\text{A}^-$; $-\text{S}^+\text{R}^9\text{R}^{10}\text{A}^-$; and carbohydrate residue;

- [178] wherein the R^{13} , R^{14} , and R^{15} ($\text{C}_1\text{-C}_{10}$)alkyl; halo($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_3\text{-C}_{10}$)cycloalkyl; polyalkyl; ($\text{C}_2\text{-C}_{10}$)alkenyl; ($\text{C}_2\text{-C}_{10}$)alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; aryl($\text{C}_1\text{-C}_{10}$)alkyl; heterocyclyl($\text{C}_1\text{-C}_{10}$)alkyl; quaternary heterocyclyl($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_1\text{-C}_{10}$)alkylaryl($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_1\text{-C}_{10}$)alkylheterocyclyl($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_1\text{-C}_{10}$)alkylammonium($\text{C}_1\text{-C}_{10}$)alkyl; aminocarbonyl($\text{C}_1\text{-C}_{10}$)alkyl; ($\text{C}_1\text{-C}_{10}$)alkylaminocarbonyl($\text{C}_1\text{-C}_{10}$)alkyl; carboxy($\text{C}_1\text{-C}_{10}$)alkylaminocarbonyl($\text{C}_1\text{-C}_{10}$)alkyl; and polyether radicals optionally may have one or more carbons replaced by $-\text{O}-$; $-\text{NR}^9-$; $-\text{N}^+\text{R}^9\text{R}^{10}\text{A}^-$; $-\text{S}-$; $-\text{SO}-$; $-\text{SO}_2-$; $-\text{S}^+\text{R}^9\text{A}^-$; $-\text{PR}^9-$; $-\text{P}^+\text{R}^9\text{R}^{10}\text{A}^-$; $-\text{P}(\text{O})\text{R}^9-$; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue;
- [179] (j2) wherein R^{16} and R^{17} are independently selected from the group consisting of R^9 and M ;
- [180] (k2) wherein R^{18} is selected from the group consisting of ($\text{C}_1\text{-C}_{10}$)alkyl; heterocyclyl; quaternary heterocyclyl; aryl($\text{C}_1\text{-C}_{10}$)alkyl; acyl; and aryl($\text{C}_1\text{-C}_{10}$)alkoxycarbonyl;
- [181] wherein the R^{18} ($\text{C}_1\text{-C}_{10}$)alkyl; heterocyclyl; quaternary heterocyclyl; aryl($\text{C}_1\text{-C}_{10}$)alkyl; acyl; and aryl($\text{C}_1\text{-C}_{10}$)alkoxycarbonyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; $-\text{CN}$; oxo; $-\text{OR}^9$; $-\text{NR}^9\text{R}^{10}$; $-\text{N}^+\text{R}^9\text{R}^{11}\text{R}^{12}\text{A}^-$; $-\text{SR}^9$; $-\text{S}(\text{O})\text{R}^9$; $-\text{SO}_2\text{R}^9$; $-\text{SO}_3\text{R}^9$; $-\text{CO}_2\text{R}^9$; $-\text{CONR}^9\text{R}^{10}$; $-\text{SO}_2\text{OM}$; $-\text{SO}_2\text{NR}^9\text{R}^{10}$; $-\text{PR}^9\text{R}^{10}$; $-\text{P}(\text{OR}^{13})\text{OR}^{14}$; $-\text{PO}(\text{OR}^{16})\text{OR}^{17}$; and $-\text{C}(\text{O})\text{OM}$;
- [182] (l2) wherein R^{19} and R^{20} are independently selected from the group consisting of hydrogen and ($\text{C}_1\text{-C}_{10}$)alkyl; and

- [183] (m2) same as (m1) above;
- [184] (n2) provided that aryl is selected from the group consisting of optionally substituted phenyl, biphenyl and naphthyl;
- [185] (o2) provided that heterocyclyl is selected from the group consisting of optionally substituted heterocyclyl comprising a 4 to 10 membered ring and comprising one or more ring atoms that are heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus.
- [186] According to another embodiment, the substituents on the compounds of formulas I-1 to I-24 are as follows:
- [187] (a3) R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and $(C_1-C_{10})alkyl$;
- [188] (b3) R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen and $(C_1-C_{10})alkyl$; or
- [189] R^{3A} and R^{3B} taken together with the carbon to which they are attached form $(C_3-C_7)cycloalkyl$;
- [190] (c3) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen and $-OR^9$;
- [191] (d3) R^{5A} is selected from phenyl, wherein said phenyl is optionally substituted with one or more radicals independently selected from the group consisting of R5 halogen; hydroxy; $-NO_2$; $(C_1-C_{10})alkyl$; $halo(C_1-C_{10})alkyl$; $aryl(C_1-C_{10})alkyl$; $heterocyclyl(C_1-C_{10})alkyl$; polyether; $-OR^{13}$; $-NR^{13}R^{14}$; and $-NR^{13}C(O)R^{14}$;
- [192] (e3) R^{5B} is hydrogen;

- [193] (f3) one or more R^6 (wherein $m = 1, 2, 3$ or 4 in $(R^6)^m$) radicals are independently selected from the group consisting of hydrogen; $-NO_2$; $(C_1-C_{10})alkyl$; $halo(C_1-C_{10})alkyl$; $-OR^{13}$; $-NR^{13}R^{14}$; or
- [194] two R^6 groups attached to adjacent carbon atoms (e.g., adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C_5-C_8 mono-cyclic carbocyclic or heterocyclic ring;
- [195] wherein the mono-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; $(C_1-C_{10})alkyl$; $halo(C_1-C_{10})alkyl$; $(C_1-C_{10})alkoxy$; aryl; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-P^9R^{10}$; $-P^+R^9R^{11}R^{12}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue;
- [196] (g3) wherein R^9 , R^{10} and R^w are independently selected from the group consisting of hydrogen; $(C_1-C_{10})alkyl$; heterocyclyl; ammonium($C_1-C_{10})alkyl$; $(C_1-C_{10})alkylammonium(C_1-C_{10})alkyl$; aryl($C_1-C_{10})alkyl$; heterocyclyl($C_1-C_{10})alkyl$; carboxy($C_1-C_{10})alkyl$; carbo($C_1-C_{10})alkoxy(C_1-C_{10})alkyl$; carboxyheterocyclyl; carboxy($C_1-C_{10})alkylamino$; and acyl;
- [197] (h3) wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; $(C_1-C_{10})alkyl$; heterocyclyl; aryl($C_1-C_{10})alkyl$; carboxy($C_1-C_{10})alkyl$; and carbo($C_1-C_{10})alkoxy(C_1-C_{10})alkyl$; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring;
- [198] (i3) wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; $(C_1-C_{10})alkyl$; $halo(C_1-C_{10})alkyl$; heterocyclyl; quaternary heterocyclyl; aryl($C_1-C_{10})alkyl$; heterocyclyl($C_1-C_{10})alkyl$; quaternary heterocyclyl($C_1-C_{10})alkyl$; $(C_1-C_{10})alkylheterocyclyl(C_1-C_{10})alkyl$; $(C_1-C_{10})alkylammonium(C_1-C_{10})alkyl$; and polyether; or

- [199] wherein the R¹³, R¹⁴, and R¹⁵ (C₁-C₁₀)alkyl; halo(C₁-C₁₀)alkyl; heterocyclyl; quaternary heterocyclyl; aryl(C₁-C₁₀)alkyl; heterocyclyl(C₁-C₁₀)alkyl; quaternary heterocyclyl(C₁-C₁₀)alkyl; (C₁-C₁₀)alkylheterocyclyl(C₁-C₁₀)alkyl; (C₁-C₁₀)alkylammonium(C₁-C₁₀)alkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; (C₁-C₁₀)alkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclyl(C₁-C₁₀)alkyl; carboxy; carboxy(C₁-C₁₀)alkyl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; and -CONR⁹R¹⁰;
- [200] (j3) wherein R¹⁶ is selected from the group consisting of R⁹ and M;
- [201] (k3) same as (k2) above;
- [202] (l3) same as (l2) above;
- [203] (m3) same as (m2) above;
- [204] (n3) provided that aryl is selected from the group consisting of optionally substituted phenyl, biphenyl and naphthyl;
- [205] (o3) provided that heterocyclyl is selected from the group consisting of optionally substituted heterocyclyl comprising a 5 to 8 membered ring and comprising one or more ring atoms that are heteroatoms selected from the group consisting of oxygen, nitrogen, sulfur and phosphorus.
- [206] According to another embodiment, the substituents of formulas I-1 to I-24 are as follows:
- [207] (a4) R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl and hexyl; and
- [208] (b4) R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-

butyl, pentyl, hexyl, phenoxyethylene, phenoxypropylene, pyridinyloxymethylene, pyridinyloxyethylene; methylpyridinyloxymethylene, methylpyridinyloxyethylene, pyrimidinyloxymethylene, and pyrimidinyloxyethylene; or R^{3A} and R^{3B} taken together with the carbon to which they are attached form cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl;

- [209] (c4) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, phenyl, pyridinyl, amino, methylamino, dimethylamino, ethylamino and diethylamino;
- [210] (d4) same as (d3) above;
- [211] (e4) R^{5B} is hydrogen;
- [212] (f4) one or more R⁶ (wherein m = 1, 2, 3 or 4 in (R⁶)m) radicals are independently selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, methylthio, methylsulfinyl, methylsulfonyl, ethylthio, ethylsulfinyl, ethylsulfonyl, amino, hydroxyamino, methylamino, dimethylamino, ethylamino, diethylamino, trimethylammonium, triethylammonium, N-methyl-N-carboxymethyl-amino, N,N-dimethyl-N-carboxymethyl-ammonium, methylcarbonylamino, chloromethylcarbonylamino, fluoromethylcarbonylamino, bromomethylcarbonylamino, iodomethylcarbonylamino, ethylcarbonylamino, n-propylcarbonylamino, n-butylcarbonylamino, n-pentylcarbonylamino, n-hexylcarbonylamino, benzyloxycarbonylamino, aminoimidocarbonylamino, morpholinyl, N-methyl-morpholinium, azetidinyl, N-methyl-azetidinium, pyrrolidine, N-methyl-pyrrolidinium, piperazinyl, N-methylpiperazinyl, N,N'-dimethyl-piperazinium, piperidinyl, methylpiperidinyl, N-methyl-piperidinium, and thienyl; or

- [213] two R⁶ groups attached to adjacent carbon atoms (e.g., adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C₄-C₁₀ mono- or bi-cyclic carbocyclic or heterocyclic ring;
- [214] wherein said mono- or bi-cyclic carbocyclic or heterocyclic ring is selected from the group consisting of cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, phenyl, naphthyl, tetrahydronaphthyl, indenyl, indanyl, biphenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, triazolyl, tetrazolyl, indolizinyl, indolyl, isoindolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, furanyl, pyranyl, thiophenyl, dithioly, oxazolyl, isoxazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxazinyl, isooxazinyl, oxathioly, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxathiazinyl, chromanyl, thiochromanyl, pyrrolidinyl, imidazolidinyl, dihydrothiophenyl, dihydropyranyl, dihydrofuran, dihydrothiazolyl, dihydroindolyl, pyrrolinyl, piperidinyl, piperazinyl, morpholinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, dihydrobenzofuryl, benzothienyl, benzothiazolyl, benzothiadiazolyl, benzopyran, benzothiopyran, benzimidazolyl, benzotriazolyl, tetrazolopyridazinyl cyclohexofuryl, and cyclohexenofuryl
- [215] wherein the mono- or bi-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; methyl; ethyl; propyl; butyl; pentyl; hexyl; methoxy; ethoxy; propoxy; butoxy; pentoxy; hexyloxy; amino; methylamino; dimethylamino; ethylamino; and diethylamino; or
- [216] a pharmaceutically acceptable salt, solvate, or prodrug thereof;
- [217] (g4) same as (g3) above;
- [218] (h4) same as (h3) above;

- [219] (i4) same as (i3) above;
- [220] (j4) same as (j3) above;
- [221] (k4) same as (k3) above;
- [222] (l4) same as (l3) above;
- [223] (m4) same as (m3) above;
- [224] (n4) same as (n3) above;
- [225] (o4) same as (o3) above).

[226] According to another embodiment, the substituents on compounds of formulas I-1 to I-24 are as follows:

- [227] (a5) R^{2A} and R^{2B} are hydrogen; or
- [228] (b5) R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, and hexyl;
- [229] (c5) R^{4A} and R^{4B} are independently selected from the group consisting of hydrogen, and hydroxy;
- [230] (d5) same as (d4) above;
- [231] (e5) R^{5B} is hydrogen;
- [232] (f5) one or more R^6 (wherein m = 1, 2, 3 or 4 in $(R^6)^m$) radicals are independently selected from the group consisting of hydrogen, hydroxy, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, methoxy, ethoxy, n-propoxy, isopropoxy, methylthio, methylsulfinyl,

methylsulfonyl, ethylthio, ethylsulfinyl, ethylsulfonyl, amino, hydroxyamino, methylamino, dimethylamino, ethylamino, and diethylamino; or

- [233] two R⁶ groups attached to adjacent carbon atoms (e.g., adjacent carbon atoms on the benzo ring) together with the carbon atoms to which they are attached form a C₅-C₁₀ mono- or bi-cyclic carbocyclic or heterocyclic ring;
- [234] wherein said mono- or bi-cyclic carbocyclic or heterocyclic ring is selected from the group consisting of cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, phenyl, naphthyl, tetrahydronaphthyl, indenyl, indanyl, biphenyl, pyrrolyl, imidazolyl, pyrazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl, triazolyl, tetrazolyl, indolizinyl, indolyl, isoindolyl, purinyl, quinolyl, isoquinolyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, furanyl, pyranyl, thiophenyl, dithioly, oxazolyl, isoxazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxazinyl, isooxazinyl, oxathioly, thiazolyl, isothiazolyl, thiodiazolyl, oxathiazolyl, oxathiazinyl, chromanyl, thiochromanyl, pyrrolidinyl, imidazolidinyl, dihydrothiophenyl, dihydropyranyl, dihydrofuranyl, dihydrothiazolyl, dihydroindolyl, pyrrolinyl, piperidinyl, piperazinyl, morpholinyl, benzoxazolyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, dihydrobenzofuryl, benzothienyl, benzothiazolyl, benzothiadiazolyl, benzopyran, benzothiopyran, benzimidazolyl, benzotriazolyl, tetrazolopyridazinyl cyclohexofuryl, and cyclohexenofuryl.
- [235] wherein the mono- or bi-cyclic carbocyclic or heterocyclic rings optionally may be further substituted with one or more radicals selected from the group consisting of halogen; hydroxy; cyano; nitro; oxo; thioxo; methyl; ethyl; propyl; butyl; pentyl; hexyl; methoxy; ethoxy; propoxy; butoxy; pentoxy; hexyloxy; amino; methylamino; dimethylamino; ethylamino; and diethylamino;
- [236] (g5) same as (g4) above;
- [237] (h5) same as (h4) above;

- [238] (i5) same as (i4) above;
- [239] (j5) same as (j4) above;
- [240] (k5) same as (k4) above;
- [241] (l5) same as (l4) above; or
- [242] (m5) wherein A⁻ is a pharmaceutically acceptable anion; or a pharmaceutically acceptable salt, solvate, or prodrug thereof;
- [243] (n5) same as (n4) above;
- [244] (o5) same as (o4) above.
- [245] According to another embodiment, the substituents on compounds I-1 to I-24 are as follows:
- [246] (a6) same as (a1) above;
- [247] (b6) same as (b1) above;
- [248] (c6) same as (c1) above;
- [249] (d6) R^{5A} is selected from the group consisting of aryl; heterocyclyl; and quaternary heterocyclyl;
- [250] wherein the R^{5A} aryl; heterocyclyl; and quaternary heterocyclyl radical optionally may be substituted with one or more radicals independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -

$\text{OC(O)NR}^{13}\text{R}^{14}$; $-\text{NR}^{13}\text{SOR}^{14}$; $-\text{NR}^{13}\text{SO}_2\text{R}^{14}$; $-\text{NR}^{13}\text{SONR}^{14}\text{R}^{15}$; $-\text{NR}^{13}\text{SO}_2\text{NR}^{14}\text{R}^{15}$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P(O)R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{P(OR}^{13})\text{OR}^{14}$; $-\text{S}^+\text{R}^{13}\text{R}^{14}\text{A}^-$; and $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$;

- [251] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5A} radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclyl; -OR¹⁹; -NR¹⁹R²⁰; -SR¹⁹; -S(O)R¹⁹; -SO₂R¹⁹; -SO₃R¹⁹; -CO₂R¹⁹; -CONR¹⁹R²⁰; -N⁺R⁹R¹⁹R²⁰A⁻; -P(O)R¹⁹R²⁰; -PR¹⁹R²⁰; -P⁺R⁹R¹⁹R²⁰A⁻; and -P(O)(OR¹⁹)OR²⁰;
- [252] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclylalkyl, and polyether substituents of the R^{5A} radical optionally may have one or more carbons replaced by -O-; -NR¹⁹-; -N⁺R¹⁹R²⁰A⁻-; -S-; -SO-; -SO₂-; -S⁺R¹⁹A⁻-; -PR¹⁹-; -P(O)R¹⁹-; -P⁺R¹⁹R²⁰A⁻-; or phenylene;
- [253] (e6) same as (e1) above;
- [254] (f6) wherein R⁹, R¹⁰, and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclylalkyl; carboxyalkyl; carboalkoxyalkyl; carboxyheterocyclyl; carboxyalkylamino; and acyl;
- [255] (g6) wherein R¹¹ and R¹² are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; carboxyalkyl; carboalkoxyalkyl; cycloalkyl;

cyanoalkyl; $-OR^9$; $-NR^9R^{10}$; $-SR^9$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^9$; $-CO_2R^9$; and $-CONR^9R^{10}$; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring;

- [256] (h6) wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [257] wherein R^{13} and R^{14} together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [258] wherein R^{14} and R^{15} together with the nitrogen atom to which they are attached form a cyclic ring; and
- [259] wherein the R^{13} , R^{14} , and R^{15} alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; $-CN$; sulfo; oxo; alkyl; sulfoalkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; $-OR^{16}$; $-NR^9R^{10}$; $-N^+R^9R^{10}R^wA^-$; $-SR^{16}$; $-S(O)R^9$; $-SO_2R^9$; $-SO_3R^{16}$; $-CO_2R^{16}$; $-CONR^9R^{10}$; $-SO_2NR^9R^{10}$; $-PO(OR^{16})OR^{17}$; $-PR^9R^{10}$; $-P^+R^9R^{10}R^{11}A^-$; $-S^+R^9R^{10}A^-$; and carbohydrate residue;

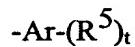
- [260] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue;
- [261] (i6) wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M; and
- [262] (j6) wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl;
- [263] wherein the R¹⁸ alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹¹R¹²A⁻; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; -CONR⁹R¹⁰; -SO₂OM; -SO₂NR⁹R¹⁰; -PR⁹R¹⁰; -P(O)R¹³OR¹⁴; -PO(OR¹⁶)OR¹⁷; and -C(O)OM;
- [264] (k6) wherein R¹⁹ and R²⁰ are independently selected from the group consisting of hydrogen and alkyl; and
- [265] (l6) same as (l1) above;
- [266] (m6) same as (m1) above.

[267] According to another embodiment, the substituents of compounds of formulas I-1 to I-24 are as follows:

[268] (a7) same as (a1) above;

[269] (b7) same as (b1) above;

[270] (c7) R^{5A} has the formula



[271] wherein t is an integer from 0 to 5; Ar is selected from the group consisting of phenyl; thiophenyl; pyridyl; piperazinyl; piperonyl; pyrrolyl; naphthyl; furanyl; anthracenyl; quinolinyl; isoquinolinyl; quinoxaliny; imidazolyl; pyrazolyl; oxazolyl; isoxazolyl; pyrimidinyl; thiazolyl; triazolyl; isothiazolyl; indolyl; benzoimidazolyl; benzoxazolyl; benzothiazolyl; and benzoisothiazolyl;

[272] one or more R^5 are independently selected from the group consisting of halogen; -CN; -NO₂; oxo; alkyl; polyalkyl; haloalkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; polyether; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻; and

- [273] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^5 radical optionally may be further substituted with one or more radicals selected from the group consisting of -CN; halogen; hydroxy; oxo; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; heterocyclalkyl; quaternary heterocyclyl; -OR¹⁹; -NR¹⁹R²⁰; -SR¹⁹; -S(O)R¹⁹; -SO₂R¹⁹; -SO₃R¹⁹; -CO₂R¹⁹; -CONR¹⁹R²⁰; -N⁺R⁹R¹⁹R²⁰A⁻; -P(O)R¹⁹R²⁰; -PR¹⁹R²⁰; -P⁺R⁹R¹⁹R²⁰A⁻; and -P(O)(OR¹⁹)OR²⁰;
- [274] wherein the alkyl, polyalkyl, haloalkyl, hydroxyalkyl, cycloalkyl, alkenyl, alkynyl, aryl, heterocyclyl, quaternary heterocyclyl, arylalkyl, heterocyclalkyl, and polyether substituents of the R^5 radical optionally may have one or more carbons replaced by -O-; -NR¹⁹-; -N⁺R¹⁹R²⁰A⁻; -S-; -SO-; -SO₂-; -S⁺R¹⁹A⁻; -PR¹⁹-; -P(O)R¹⁹-; -P⁺R¹⁹R²⁰A⁻; or phenylene;
- [275] (d7) same as (d1) above;
- [276] (e7) same as (e1) above;
- [277] (f7) wherein R^9 , R^{10} , and R^W are independently selected from the group consisting of hydrogen; alkyl; cycloalkyl; alkenyl; alkynyl; aryl; heterocyclyl; alkylammoniumalkyl; arylalkyl; heterocyclalkyl; carboxyalkyl; carboalkoxyalkyl; carboxyheterocyclyl; carboxyalkylamino; and acyl;
- [278] (g7) wherein R^{11} and R^{12} are independently selected from the group consisting of hydrogen; -CN; halogen; oxo; alkyl; alkenyl; alkynyl; aryl; heterocyclyl; arylalkyl; carboxyalkyl; carboalkoxyalkyl; cycloalkyl; cyanoalkyl; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; and -CONR⁹R¹⁰; or R^{11} and R^{12} together with the carbon atom to which they are attached form a cyclic ring; and

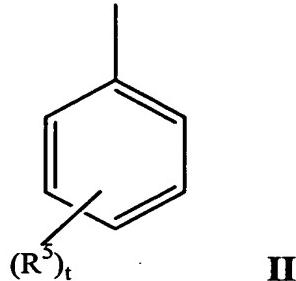
- [279] (h7) wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen; alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; carboxyalkylaminocarbonylalkyl; and polyether; or
- [280] wherein R¹³ and R¹⁴ together with the nitrogen atom to which they are attached form a mono- or polycyclic heterocyclyl that is optionally substituted with one or more radicals selected from the group consisting of oxo, carboxy, and quaternary salts; or
- [281] wherein R¹⁴ and R¹⁵ together with the nitrogen atom to which they are attached form a cyclic ring; and
- [282] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl; alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; sulfo; oxo; alkyl; sulfoalkyl; heterocyclyl; quaternary heterocyclyl; quaternary heterocyclylalkyl; carboxy; carboxyalkyl; guanidinyl; -OR¹⁶; -NR⁹R¹⁰; -N⁺R⁹R¹⁰R^wA⁻; -SR¹⁶; -S(O)R⁹; -SO₂R⁹; -SO₃R¹⁶; -CO₂R¹⁶; -CONR⁹R¹⁰; -SO₂NR⁹R¹⁰; -PO(OR¹⁶)OR¹⁷; -PR⁹R¹⁰; -P⁺R⁹R¹⁰R¹¹A⁻; -S⁺R⁹R¹⁰A⁻; and carbohydrate residue; and
- [283] wherein the R¹³, R¹⁴, and R¹⁵ alkyl; haloalkyl; cycloalkyl; polyalkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; quaternary heterocyclylalkyl; alkylarylalkyl; alkylheterocyclylalkyl; alkylammoniumalkyl; aminocarbonylalkyl;

alkylaminocarbonylalkyl; carboxyalkylaminocarbonylalkyl; and polyether radicals optionally may have one or more carbons replaced by -O-; -NR⁹-; -N⁺R⁹R¹⁰A⁻; -S-; -SO₂-; -S⁺R⁹A⁻; -PR⁹-; -P⁺R⁹R¹⁰A⁻; -P(O)R⁹-; phenylene; carbohydrate residue; amino acid residue; peptide residue; or polypeptide residue;

- [284] (i7) wherein R¹⁶ and R¹⁷ are independently selected from the group consisting of R⁹ and M;
- [285] (j7) wherein R¹⁸ is selected from the group consisting of alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl;
- [286] wherein the R¹⁸ alkyl; alkenyl; alkynyl; aryl; heterocyclyl; quaternary heterocyclyl; arylalkyl; heterocyclylalkyl; acyl; alkoxy carbonyl; arylalkoxy carbonyl; and heterocyclylalkoxy carbonyl radical optionally may be substituted with one or more radicals selected from the group consisting of halogen; -CN; oxo; -OR⁹; -NR⁹R¹⁰; -N⁺R⁹R¹¹R¹²A⁻; -SR⁹; -S(O)R⁹; -SO₂R⁹; -SO₃R⁹; -CO₂R⁹; -CONR⁹R¹⁰; -SO₂OM; -SO₂NR⁹R¹⁰; -PR⁹R¹⁰; -P(O)R¹³OR¹⁴; -PO(OR¹⁶)OR¹⁷; and -C(O)OM;
- [287] (k7) wherein R¹⁹ and R²⁰ are independently selected from the group consisting of hydrogen and alkyl;
- [288] (l7) same as (l1) above;
- [289] (m7) same as (m1) above.
- [290] According to another embodiment, the substituents of compounds of formulas I-1 to I-24 are as follows:
- [291] (a8) same as (a7) above;

[292] (b8) same as (b7) above;

[293] (c8) wherein R^{5A} is:



wherein R⁵ is as defined in (c7) above and t is 1, 2, 3, 4 or 5;

[294] (d8) same as (d7) above;

[295] (e8) same as (e7) above;

[296] (f8) same as (f7) above;

[297] (g8) same as (g7) above;

[298] (h8) same as (h7) above;

[299] (i8) same as (i7) above;

[300] (j8) same as (j7) above;

[301] (k8) same as (k7) above;

[302] (l8) same as (l7) above;

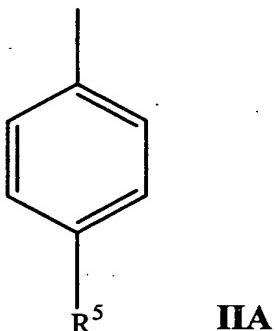
[303] (m8) same as (m7) above.

[304] According to another embodiment, the substituents of compounds of formulas I-1 to I-24 are as follows:

[305] (a9) same as (a8) above;

[306] (b9) same as (b8) above;

[307] (c9) wherein R^{5A} is:



wherein R⁵ is as defined in (c8) above;

[308] (d9) same as (d8) above;

[309] (e9) same as (e8) above;

[310] (f9) same as (f8) above;

[311] (g9) same as (g8) above;

[312] (h9) same as (h8) above;

[313] (i9) same as (i8) above;

[314] (j9) same as (j8) above;

[315] (k9) same as (k8) above;

[316] (l9) same as (l8) above;

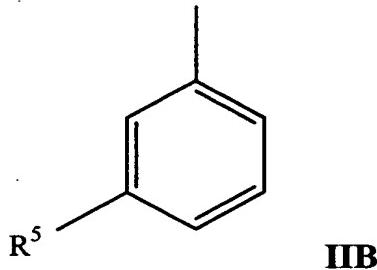
[317] (m9) same as (m8) above.

[318] According to another embodiment, the substituents of compounds of formulas I-1 to I-24 are as follows:

[319] (a10) same as (a8) above;

[320] (b10) same as (b8) above;

[321] (c10) wherein R^{5A} is:



wherein R⁵ is as defined in (c8) above;

[322] (d10) same as (d9) above;

[323] (e10) same as (e9) above;

[324] (f10) same as (f9) above;

[325] (g10) same as (g9) above;

[326] (h10) same as (h9) above;

[327] (i10) same as (i9) above;

[328] (j10) same as (j9) above;

[329] (k10) same as (k9) above;

[330] (l10) same as (l9) above;

[331] (m10) same as (m9) above.

- [332] Preferably, in each of the various embodiments of the invention described above, in each of Formulas I-1 to I-24 and in each of the benzothiepine intermediates and products (containing a benzothiepene 7 membered ring described in Schemes 1 – 7), at least one or more of the following conditions are satisfied:
- [333] (1) j is 1 or 2. Preferably, j is 2; and/or
- [334] (2) The substituents at the 2-position of the benzothiepine are independently selected from the group consisting of hydrogen and alkyl. Preferably, these substituents are hydrogen; and/or
- [335] (3) The substituents at the 3-position of the benzothiepine are independently selected from the group consisting of hydrogen and alkyl. Preferably, these substituents are independently selected from the group consisting of C₁₋₆ alkyls. More preferably, these substituents are selected from the group consisting of ethyl, propyl and butyl. Still more preferably, either (a) one of these 3-position substituents is ethyl and the other is n-butyl, or (b) both of these 3-position substituents are n-butyl; and/or
- [336] (4) The substituents at the 5-position of the benzothiepene is aryl or substituted aryl. Preferably, the aryl is phenyl that is optionally substituted at the meta and/or the para position. More preferably, the substitution at the meta and/or the para position of the phenyl is glucuronidated or monosubstituted with a radical selected from the group consisting of -R⁵, -OR¹³, -NR¹³C(O)R¹⁴, -NR¹³C(O)NR¹⁴R¹⁵, -NR¹³CO₂R¹⁴, -OC(O)R¹³, -OC(O)NR¹³R¹⁴, -NR¹³SOR¹⁴, -NR¹³SO₂R¹⁴, -NR¹³SONR¹⁴R¹⁵, and -NR¹³SO₂NR¹⁴R¹⁵ wherein R⁵, R¹³, R¹⁴ and R¹⁵ are as previously defined; and/or
- [337] (6) Only one of R^{5A} or R^{5B} is hydrogen; and/or
- [338] (7) One or more substituents R⁶ of the benzo ring of the benzothiepine are independently selected from the group consisting of halogen, -OR¹³ and -NR¹³R¹⁴, wherein R¹³ and R¹⁴ are as previously defined. Preferably, the

substituents of the benzo ring are independently selected from the group consisting of halogen, hydroxy, alkoxy, amino, alkylamino and dialkylamino. Still more preferably, the substituents are independently selected from the group consisting of chloro, methoxy and dimethylamino.

[339] Alternative Forms Of Novel Compounds

[340] Also included in the family of compounds of Formulas I-1 to I-24 are (a) the stereoisomers thereof, (b) the pharmaceutically-acceptable salts thereof, (c) the tautomers thereof, (d) the protected acids and the conjugate acids thereof, and (e) the prodrugs thereof.

[341] (a) The Stereoisomers

[342] The stereoisomers of these compounds may include, but are not limited to, enantiomers, diastereomers, racemic mixtures and combinations thereof. Such stereoisomers can be prepared and separated using conventional techniques, either by reacting enantiomeric starting materials, or by separating isomers of compounds of the present invention. Isomers may include geometric isomers. Examples of geometric isomers includes, but are not limited to, cis isomers or trans isomers across a double bond. Other isomers are contemplated among the compounds of the present invention. The isomers may be used either in pure form or in admixture with other isomers of the inhibitors described above.

[343] (b) The Pharmaceutically-Acceptable Salts

[344] Pharmaceutically-acceptable salts of the compounds of the present invention (Formulas I-1 to I-24) include salts commonly used to form alkali metal salts or form addition salts of free acids or free bases. The nature of the salt is not critical, provided that it is pharmaceutically-acceptable. Suitable pharmaceutically-acceptable acid addition salts of compounds of Formulas I-1 to I-24 may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic,

nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids. Examples of organic and sulfonic classes of organic acids includes, but are not limited to, formic, acetic, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric, ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, salicyclic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic, sulfanilic, cyclohexylaminosulfonic, stearic, algenic, N-hydroxybutyric, salicyclic, galactaric and galacturonic acid and combinations thereof.

- [345] Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I-1 to I-24 include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, and trimethylamine. The above salts may be prepared by conventional means from the corresponding compounds of the invention by reacting, for example, the appropriate acid or base with the compounds of Formulas I-1 to I-24.

[346] (c) The Tautomers

- [347] Tautomers of the aforementioned compounds (Formulas I-1 to I-24) are encompassed by the present invention. Thus, for example, (even though not shown) a carbonyl includes its hydroxy tautomer.

[348] (d) The Protected Acids and the Conjugate Acids

- [349] The protected acids of these compounds (Formulas I-1 to I-24) include, but are not limited to, protected acids such as esters, hydroxyamino derivatives, amides and sulfonamides. Thus, for example, primary and secondary amines

can be reacted with carboxylic acid substituted forms of the compounds of Formulas I-1 to I-24 to form amides which can be useful as prodrugs. Preferred amines are heterocyclicamines, including optionally substituted aminothiazoles, optionally substituted amino-isoxazoles, optionally substituted aminopyridines, optionally substituted aniline derivatives, optionally substituted sulfonamides, optionally substituted aminocarboxylic acids, and the like. The esters, hydroxyamino derivatives and sulfonamides can be prepared from the acids by methods known to one skilled in the art.

[350] (e) The Prodrugs

[351] The present invention includes the prodrugs of the compounds of Formulas I-1 to I-24.

[352] Dosages And Treatment Regimen

[353] Dosage levels of the compounds of Formulae I-1 to I-24 typically are from about 0.001 mg to about 10,000 mg daily, preferably from about 0.005 mg to about 1,000 mg daily, more preferably from about 0.008 mg to about 100 mg daily, and even more preferably from about 0.05 mg to about 50 mg daily. On the basis of mg/kg daily dose, either given in a single or divided doses, dosages typically range from about 0.001/75 mg/kg to about 10,000/75 mg/kg, preferably from about 0.005/75 mg/kg to about 1,000/75 mg/kg, more preferably from about 0.008/75 to about 100/75 mg/kg, and even more preferably from about 0.05/75 mg/kg to about 50/75 mg/kg.

[354] The total daily dose of each drug can be administered to the patient in a single dose, or in multiple subdoses. Typically, subdoses can be administered two to six times per day, preferably two to four times per day, and even more preferably two to three times per day. Doses can be in immediate release form or sustained release form sufficiently effective to obtain the desired control over the hyperlipidemic condition.

- [355] The dosage regimen to prevent, treat, give relief from, or ameliorate a hyperlipidemic condition or disorder, or to otherwise protect against or treat high cholesterol blood (or plasma) levels with the combinations and compositions of the present invention is selected in accordance with a variety of factors. These factors include, but are not limited to, the type, age, weight, sex, diet, and medical condition of the subject, the severity of the disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular inhibitors employed, whether a drug delivery system is utilized, and whether the inhibitors are administered with other active ingredients. Thus, the dosage regimen actually employed may vary widely and therefore deviate from the preferred dosage regimen set forth above.
- [356] Initial treatment of a patient suffering from a hyperlipidemic condition or disorder can begin with the dosages indicated above. Treatment generally should be continued as necessary over a period of several weeks to several months or years until the hyperlipidemic condition or disorder has been controlled or eliminated. Patients undergoing treatment with the combinations of the compounds disclosed herein can be routinely monitored, for example, by measuring serum LDL and total cholesterol levels by any of the methods well-known in the art, to determine the effectiveness of the combination therapy. Continuous and intermittent analysis of such data permits modification of the treatment regimen during therapy so that optimal therapeutically effective amounts of each type of inhibitor are administered at any time for an appropriate duration of time. In this way, the treatment regimen/dosing schedule can be rationally modified over the course of therapy so that the lowest amount of inhibitor that exhibits satisfactory therapeutic effectiveness is administered, and so that administration is continued only so long as is necessary to successfully treat or otherwise ameliorate the hyperlipidemic condition. Of course, maintenance dosing to keep the hyperlipidemic condition under the desired control may be instituted as necessary.

[357] Pharmaceutical Compositions

- [358] For the prophylaxis or treatment of the conditions and disorders referred to above, the compounds of this invention (Formulas I-1 to I-24) can be administered as the compound *per se*. Alternatively, pharmaceutically-acceptable salts are particularly suitable for medical applications because of their greater aqueous solubility relative to that of the parent compound.
- [359] The compounds of the present invention also can be administered with an acceptable carrier in the form of a pharmaceutical composition. The carrier must be acceptable in the sense of being compatible with the other ingredients of the composition and must not be intolerably deleterious to the recipient. The carrier can be a solid or a liquid, or both, and preferably is formulated with the compound as a unit-dose composition, for example, a tablet, which can contain from about 0.05% to about 95% by weight of the active compound(s) based on a total weight of the dosage form. Other pharmacologically active substances can also be present, including other compounds useful in the treatment of a hyperlipidemic condition.
- [360] The active compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a therapeutically effective dose for the treatment intended. The active compounds and compositions, for example, may be administered orally, sublingually, nasally, pulmonarily, mucosally, parenterally, intravascularly, intraperitoneally, subcutaneously, intramuscularly or topically. Unit dose formulations, particularly orally administrable unit dose formulations such as tablets or capsules, generally contain, for example, from about 0.001 to about 500 mg, preferably from about 0.005 mg to about 100 mg, and more preferably from about 0.01 to about 50 mg, of the active ingredient. In the case of pharmaceutically acceptable salts, the weights indicated above for the active ingredient refer to the weight of the pharmaceutically active ion derived from the salt.

- [361] For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet, a capsule, a suspension, an emulsion, a paste, a solution, a syrup or other liquid form. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. If administered by mouth, the compounds may be admixed with, for example, lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration.
- [362] Oral delivery of the compounds of the present invention can include formulations, as are well known in the art, to provide immediate delivery or prolonged or sustained delivery of the drug to the gastrointestinal tract by any number of mechanisms. Immediate delivery formulations include, but are not limited to, oral solutions, oral suspensions, fast-dissolving tablets or capsules, sublingual tablets, disintegrating tablets and the like. Prolonged or sustained delivery formulations include, but are not limited to, pH sensitive release of the active ingredient from the dosage form based on the changing pH of the small intestine, slow erosion of a tablet or capsule, retention in the stomach based on the physical properties of the formulation, bioadhesion of the dosage form to the mucosal lining of the intestinal tract, or enzymatic release of the active drug from the dosage form. The intended effect is to extend the time period over which the active drug molecule is delivered to the site of action (for example, the ileum for ASBT inhibitors) by manipulation of the dosage form. Thus, enteric-coated and enteric-coated controlled release formulations are within the scope of the present invention. Suitable enteric coatings include cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethylcellulose phthalate and anionic polymers of methacrylic acid and methacrylic acid methyl ester. Such prolonged or sustained delivery formulations preferably are in a dispersed form at the time they reach the ileum. Other examples of suitable coatings include products known as Eudragit S provided

in a thickness sufficient to release the active ingredient in the desired location of the GI tract. Preferably, in the case of an Eudragit S coating, the coating has a thickness from about 10 to about 50 microns, more preferably from about 20 to 45 microns, even more preferably from about 25 to about 43 microns and most preferably from about 30 to about 40 microns. The coating of Eudragit S may be combined with other coating materials known as Eudragit L. Formulations of ASBT inhibitor(s), such as tablets coated with Eudragit S and/or Eudragit L, can be readily formed by those of ordinary skill.

- [363] Pharmaceutical compositions suitable for oral administration can be presented in discrete units, such as capsules, cachets, lozenges, or tablets, each containing a predetermined amount of at least one compound of the present invention; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water or water-in-oil emulsion. As indicated, such compositions can be prepared by any suitable method of pharmacy which includes the step of bringing into association the inhibitor(s) and the carrier (which can constitute one or more accessory ingredients). In general, the compositions are prepared by uniformly and intimately admixing the inhibitor(s) with a liquid or finely divided solid carrier, or both, and then, if necessary, shaping the product. For example, a tablet can be prepared by compressing or molding a powder or granules of the inhibitors, optionally with one or more accessory ingredients. Compressed tablets can be prepared by compressing, in a suitable machine, the compound in a free-flowing form, such as a powder or granules optionally mixed with a binder, lubricant, inert diluent and/or surface active/dispersing agent(s). Molded tablets can be made, for example, by molding the powdered compound in a suitable machine.
- [364] Liquid dosage forms for oral administration can include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

- [365] Pharmaceutical compositions suitable for buccal (sub-lingual) administration include lozenges comprising a compound of the present invention in a flavored base, usually sucrose, and acacia or tragacanth, and pastilles comprising the inhibitors in an inert base such as gelatin and glycerin or sucrose and acacia.
- [366] Formulations for parenteral administration, for example, may be in the form of aqueous or non-aqueous isotonic sterile injection solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.
- [367] Pharmaceutically acceptable carriers encompass all the foregoing and the like. The pharmaceutical compositions of the invention can be prepared by any of the well-known techniques of pharmacy, such as admixing the components. The above considerations in regard to effective formulations and administration procedures are well known in the art and are described in standard textbooks. Formulation of drugs is discussed in, for example, Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania (1975); Liberman, *et al.*, Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y. (1980); and Kibbe, *et al.*, Eds., Handbook of Pharmaceutical Excipients (3rd Ed.), American Pharmaceutical Association, Washington (1999); U.S. Pharmacopeia (Twenty-First Revision – USP XXI) National Formulary (Sixteenth Edition – XVI), United States Pharmacopeial Convention, Inc., Rockville, MD (1985) and its later editions; and Remington's Pharmaceutical Sciences, 16th Edition, Arthur Osol, Editor and Chairman of the Editorial Board, Mack Publishing Co., Easton, PA (1980) and its later editions.

[368] Methods Of Use

- [369] The present invention also includes methods for the treatment of one or more hyperlipidemic condition(s) in a subject. One such method comprises the step of administering to a subject in need thereof, a therapeutically effective amount of one or more compounds of Formulas I-1 to I-24.
- [370] The present invention further includes methods for the treatment of gallstones in a subject. An exemplary method for the treatment of gallstones comprises the step of administering to a subject in need thereof, a therapeutically effective amount of one or more compound(s) of Formulas I-1 to I-24.
- [371] The methods and compounds of the present invention may be used alone or in conjunction with additional therapies and/or compounds known to those skilled in the art in the prevention or treatment of hyperlipidemia. Alternatively, the methods and compounds described herein may be used, partially or completely, in conjunctive therapy. By way of example, the compounds may be administered alone or in conjunction with other anti-hyperlipidemic agents, such as together with HMG-Co-A reductase inhibitors, bile acid sequestering agents, fibric acid derivatives, nicotinic acid, and/or probucol. The above-noted combination therapeutic agents may be provided in a kit.

[372] Terms

- [373] As used herein, various terms are defined below.
- [374] When introducing elements of the present invention or the preferred embodiment(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.
- [375] The term "subject" as used herein includes mammals (*e.g.*, humans and animals).

- [376] The term "treatment" includes any process, action, application, therapy, or the like, for improving the subject's medical condition, directly or indirectly, including, but not limited to, hyperlipidemia or conditions associated with hyperlipidemia.
- [377] The terms "prophylaxis" and "prevention" include either preventing the onset of a clinically evident hyperlipidemic condition or disorder altogether or preventing the onset of a preclinically evident stage of a hyperlipidemic condition or disorder in an individual. These terms encompass the prophylactic treatment of a subject at risk of developing a hyperlipidemic condition or disorder such as, but not limited to, atherosclerosis and hypercholesterolemia.
- [378] The term "combination therapy" or "co-therapy" means the administration of two or more therapeutic agents to treat a hyperlipidemic condition and/or disorder, for example atherosclerosis and hypercholesterolemia. Such administration encompasses co-administration of two or more therapeutic agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of active ingredients or in multiple, separate capsules for each inhibitor agent. In addition, such administration encompasses use of each type of therapeutic agent in a sequential manner. In either case, the treatment regimen will provide beneficial effects of the drug combination in treating the hyperlipidemic condition.
- [379] The phrase "therapeutically-effective" means the amount of each agent administered that will achieve the goal of improvement in hyperlipidemic condition or disorder severity, while avoiding or minimizing adverse side effects associated with the given therapeutic treatment.
- [380] The term "pharmaceutically acceptable" means that the subject item is appropriate for use in a pharmaceutical product.
- [381] The term "prodrug" includes a compound that is a drug precursor that, following administration to a subject and subsequent absorption, is converted

to an active species *in vivo*. Conversion to the active, species *in vivo* is typically via some process, such as metabolic conversion. An example of a prodrug is an acylated form of the active compound.

- [382] The term “ASBT inhibitor” includes a compound capable of inhibiting absorption of bile acids from the intestine into the circulatory system of a mammal, indicating that of a human. This includes increasing the fecal excretion of bile acids, as well as reducing the blood plasma or serum concentrations of cholesterol and cholesterol ester, and more specifically, reducing LDL and VLDL cholesterol.
- [383] Where the term “alkyl” is used, either alone or within other terms such as “haloalkyl”, and “hydroxyalkyl”, it includes linear or branched radicals having one to about twenty carbon atoms, preferably, one to about twelve carbon atoms, more preferably, “lower alkyl” radicals having one to about six carbon atoms and, even more preferably, lower alkyl radicals having one to three carbon atoms.. Examples of such radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl and the like.
- [384] Where the term “alkenyl” is used, either alone or within other terms such as “arylalkenyl”, it includes linear or branched radicals having at least one carbon-carbon double bond in a radical having from two to about twenty carbon atoms, preferably, from two to about twelve carbon atoms, and more preferably “lower alkenyl” radicals having from two to about six carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl.
- [385] The terms “alkenyl” and “lower alkenyl”, include radicals having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations.
- [386] The term “alkynyl” includes, but is not limited to, linear or branched radicals having from two to about twenty carbon atoms or, preferably, from two to about twelve carbon atoms, more preferably “lower alkynyl” radicals having

from two to about ten carbon atoms, most preferably lower alkynyl radicals having from two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

- [387] The term "cycloalkyl" includes, but is not limited to, saturated carbocyclic radicals having from three to about twelve carbon atoms, more preferably "lower cycloalkyl" radicals having from three to about ten carbon atoms. Examples of such radicals include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The term "cycloalkyl" additionally encompasses spiro systems wherein the cycloalkyl ring has a carbon ring atom in common with the seven-membered heterocyclic ring of the benzothiepene.
- [388] The term "cycloalkenyl" includes, but is not limited to, unsaturated carbocyclic radicals having at least one double bond and having from three to twelve carbon atoms and more preferably "lower cycloalkenyl" radicals having from four to about ten carbon atoms. Cycloalkenyl radicals that are partially unsaturated carbocyclic radicals that contain two double bonds (that may or may not be conjugated) can be called "cycloalkyldienyl". Examples of cycloalkenyl radicals includes, but is not limited to, cyclobutenyl, cyclopentenyl and cyclohexenyl.
- [389] The terms "halo" and "halogen" include, but are not limited to, halogen atoms such as fluorine, chlorine, bromine or iodine. The term "haloalkyl" includes radicals wherein any one or more of the alkyl carbon atoms is substituted with a halogen atom. Specifically embraced are monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals. A monohaloalkyl radical, for one example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same or different halogen atoms. "Lower haloalkyl" includes radicals having one to six carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and

dichloropropyl. "Perfluoroalkyl" includes alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

- [390] The term "hydroxyalkyl" includes, but is not limited to, linear or branched alkyl radicals preferably having from one to about ten carbon atoms, more preferably "lower hydroxyalkyl" radicals having from one to six carbon atoms and even more preferably lower hydroxyalkyl radicals having from one to three carbon atoms wherein one or more of the carbon atoms are substituted with one or more hydroxyl radicals. Examples of such radicals include hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl and hydroxyhexyl.
- [391] The term "aryl" includes, but is not limited to, a carbocyclic aromatic system containing one or more rings wherein such rings may be attached together in a pendent manner or may be fused. The term "aryl" includes aromatic radicals such as cyclopentadienyl phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, and anthracenyl. Further, "aryl" group may optionally have from one to three substituents such as lower alkyl, hydroxy, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino.
- [392] The term "heterocyclyl" includes, but is not limited to, saturated, partially saturated and unsaturated heteroatom-containing ring-shaped radicals, where the heteroatoms may be nitrogen, sulfur, oxygen or combinations thereof. Preferred heterocycls include, but are not limited to, 3-10 membered ring heterocyclyl, particularly 5-8 membered, ring heterocyclyl. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms (e.g., pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl); saturated 3 to 6-membered heteromonocyclic groups containing from 1 to 2 oxygen atoms and from 1 to 3 nitrogen atoms (e.g., morpholinyl); saturated 3 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (e.g., thiazolidinyl). Examples of partially saturated heterocyclyl

radicals include dihydrothiophene, dihydropyran, dihydrofuran and dihydrothiazole. Examples of unsaturated heterocyclic radicals, also termed "heteroaryl" radicals, include unsaturated 5 to 6 membered heteromonocyclic groups containing 1 to 4 nitrogen atoms, for example, pyrrolinyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (*e.g.*, 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl); unsaturated condensed heterocyclic groups containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl (*e.g.*, tetrazolo [1,5-b]pyridazinyl); unsaturated 3 to 6-membered heteromonocyclic groups containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic groups containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, isoxazolyl, oxadiazolyl (*e.g.*, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms (*e.g.*, benzoxazolyl, benzoxadiazolyl); unsaturated 5 to 6-membered heteromonocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl (*e.g.*, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl); unsaturated condensed heterocyclic groups containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms (*e.g.*, benzothiazolyl, benzothiadiazolyl) and the like. The term also includes radicals where heterocyclic radicals are fused with aryl radicals. Examples of such fused bicyclic radicals include benzofuran, benzothiophene, and the like. The "heterocyclyl" group may optionally have 1 to 3 substituents such as lower alkyl, hydroxy, oxo, amino and lower alkylamino. The term "heterocyclyl" includes all positioned isomers.

- [393] "Heteroaryl" radicals can include, but are not limited to, fused or unfused radicals, particularly 3-10 membered fused or unfused radicals. Preferred examples of heteroaryl radicals include benzofuryl, 2,3-dihydrobenzofuryl,

benzothienyl, indolyl, dihydroindolyl, chromanyl, benzopyran, thiochromanyl, benzothiopyran, benzodioxolyl, benzodioxanyl, pyridyl, thienyl, thiazolyl, furyl, and pyrazinyl. More preferred heteroaryl radicals are 5- or 6-membered heteroaryl, containing one or two heteroatoms selected from sulfur, nitrogen and oxygen such as thienyl, furanyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, pyridyl, piperidinyl or pyrazinyl. The term "heteroaryl" includes, but is not limited to, a fully unsaturated heterocyclyl. The term "heteroaryl" includes all positional isomers.

- [394] In either the "heterocyclyl" or the "heteroaryl" radical, the point of attachment to the molecule of interest can be at the heteroatom or elsewhere within the ring.
- [395] The term "triazolyl" includes, but is not limited to, all positional isomers. In all other heterocyclyl and heteroaryl which contain more than one ring heteroatom and for which isomers are possible, such isomers are included in the definition of said heterocyclyl and heteroaryl.
- [396] The term "quaternary heterocyclyl" includes, but is not limited to, a heterocyclyl in which one or more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or oxygen, has such a number of bonds that it is positively charged (and therefore the term is intended to encompass both ternary and quaternary positively charged structures). The point of attachment of the quaternary heterocyclyl to the molecule of interest can be at a heteroatom or elsewhere.
- [397] The term "quaternary heteroaryl" includes, but is not limited to, a heteroaryl in which one or more of the heteroatoms, for example, nitrogen, sulfur, phosphorus or oxygen, has such a number of bonds that it is positively charged (and therefore the term is intended to encompass both ternary and quaternary positively charged structures). The point of attachment of the quaternary heteroaryl to the molecule of interest can be at a heteroatom or elsewhere.
- [398] The term "oxo" includes, but is not limited to, an oxygen with two bonds.

- [399] The term "polyalkyl" includes, but is not limited to, a branched or straight hydrocarbon chain having a molecular weight up to about 20,000 gms, more preferably up to about 10,000 gms, and most preferably up to about 5,000 gms.
- [400] The term "polyether" includes, but is not limited to, a polyalkyl wherein one or more carbons are replaced by oxygen, wherein the polyether has a molecular weight up to about 20,000 gms, more preferably up to about 10,000 gms, and most preferably up to about 5,000 gms.
- [401] The term "polyalkoxy" includes, but is not limited to, a polymer of alkylene oxides, wherein the polyalkoxy has a molecular weight up to about 20,000 gms, more preferably up to about 10,000 gms, and most preferably up to about 5,000 gms.
- [402] The term "carbohydrate residue" includes, but is not limited to, residues derived from carbohydrates, but is not limited to, mono-, di-, tri-, tetra- and polysaccharides wherein the polysaccharides can have a molecular weight of up to about 20,000 gms, for example, hydroxypropyl-methylcellulose or chitosan residue; compounds derived from aldoses and ketoses with from 3 to 7 carbon atoms and which belong to the D- or L-series; aminosugars; sugar alcohols; and saccharic acids. Nonlimiting specific examples of such carbohydrates include glucose, mannose, fructose, galactose, ribose, erythrose, glycerinaldehyde, sedoheptulose, glucosamine, galactosamine, glucoronic acid, galacturonic acid, gluconic acid, galactonic acid, mannoic acid, glucamine, 3-amino-1,2-propanediol, glucaric acid and galactaric acid.
- [403] The term "peptide residue" includes, but is not limited to, polyamino acid residue containing up to about 100 amino acid units.
- [404] The term "polypeptide residue" includes, but is not limited to, a polyamino acid residue containing from about 100 amino acid units to about 1000 amino acid units, more preferably from about 100 amino acid units to about 750.

amino acid units, and even more preferably from about 100 amino acid units to about 500 amino acid units.

- [405] The term "alkylammoniumalkyl" includes, but is not limited to, an -NH₂ group or a mono-, di- or tri-substituted amino group, any of which is bonded to an alkyl wherein said alkyl is bonded to the molecule of interest.
- [406] The term "sulfo" includes, but is not limited to, a -SO₂- group, a -SO₃H group, and its salts.
- [407] The term "sulfoalkyl" includes, but is not limited to, an alkyl group to which a sulfonate group is bonded, wherein said alkyl is bonded to the molecule of interest.
- [408] The term "aralkyl" includes, but is not limited to, aryl-substituted alkyl radicals, preferably "lower aralkyl" radicals having aryl radicals attached to alkyl radicals having from one to six carbon atoms, and even more preferably lower aralkyl radicals having phenyl attached to alkyl portions having from one to three carbon atoms. Examples of such radicals include benzyl, diphenylmethyl and phenylethyl. The aryl in said aralkyl may be optionally substituted with halo, alkyl, alkoxy, haloalkyl and haloalkoxy. The term "arylalkenyl" includes aryl-substituted alkenyl radicals. Preferable arylalkenyl radicals are "lower arylalkenyl" radicals having aryl radicals attached to alkenyl radicals having from one to ten carbon atoms.
- [409] The term "heterocyclalkyl" includes, but is not limited to, an alkyl radical that is substituted with one or more heterocycl groups. Preferable heterocyclalkyl radicals are "lower heterocyclalkyl" radicals having from one or more heterocycl groups attached to an alkyl radical having from one to ten carbon atoms.
- [410] The term "heteroarylalkyl" includes, but is not limited to, an alkyl radical that is substituted with one or more heteroaryl groups. Preferable heteroarylalkyl radicals are "lower heteroarylalkyl" radicals having from one or more

heteroaryl groups attached to an alkyl radical having from one to ten carbon atoms.

- [411] The term “quaternary heterocyclalkyl” includes, but is not limited to, an alkyl radical that is substituted with one or more quaternary heterocycl groups. Preferable quaternary heterocyclalkyl radicals are “lower quaternary heterocyclalkyl” radicals having from one or more quaternary heterocycl groups attached to an alkyl radical having from one to ten carbon atoms.
- [412] The term “quaternary heteroarylalkyl” includes, but is not limited to, an alkyl radical that is substituted with one or more quaternary heteroaryl groups. Preferable quaternary heteroarylalkyl radicals are “lower quaternary heteroarylalkyl” radicals having from one or more quaternary heteroaryl groups attached to an alkyl radical having from one to ten carbon atoms.
- [413] The term “alkylheteroarylalkyl” includes, but is not limited to, a heteroarylalkyl radical that is substituted with one or more alkyl groups. Preferable alkylheteroarylalkyl radicals are “lower alkylheteroarylalkyl” radicals with alkyl portions having from one to ten carbon atoms.
- [414] The term “alkoxy” includes, but is not limited to, an alkyl radical which is attached to the molecule of interest by oxygen, such as a methoxy radical. More preferred alkoxy radicals are “lower alkoxy” radicals having from one to six carbon atoms. Examples of such radicals include methoxy, ethoxy, propoxy, iso-propoxy, butoxy and tert-butoxy.
- [415] The term “carboxy” includes, but is not limited to, the carboxy group, -CO₂H, and its salts.
- [416] The term “carboxyalkyl” includes, but is not limited to, an alkyl radical that is substituted with one or more carboxy groups. Preferable carboxyalkyl radicals are “lower carboxyalkyl” radicals having one or more carboxy groups attached to an alkyl radical having from one to six carbon atoms.

- [417] The term “carboxyheterocycl” includes, but is not limited to, a heterocycl radical that is substituted with one or more carboxy groups.
- [418] The term “carboxyheteroaryl” includes, but is not limited to, a heteroaryl radical that is substituted with one or more carboxy groups.
- [419] The term “carboalkoxyalkyl” includes, but is not limited to, an alkyl radical that is substituted with one or more alkoxy carbonyl groups. Preferable carboalkoxyalkyl radicals are “lower carboalkoxyalkyl” radicals having one or more alkoxy carbonyl groups attached to an alkyl radical having from one to six carbon atoms.
- [420] The term “carboxyalkylamino” includes, but is not limited to, an amino radical that is mono- or di-substituted. When used in combination, for example “alkylaryl” or “arylalkyl,” the individual terms “alkyl” and “aryl” listed above have the meaning indicated above.
- [421] The term “acyl” includes, but is not limited to, an organic acid group in which the hydroxy of the carboxy group has been removed. Examples of acyl groups include, but are not limited to, acetyl and benzoyl.
- [422] The term “hydrocarbyl” refers to radicals consisting exclusively of the elements carbon and hydrogen. These radicals include, for example, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties. These radicals also include alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, and aryl moieties substituted with other aliphatic or cyclic hydrocarbon groups, such as alkaryl, alkenaryl and alkynaryl. Preferably, these moieties comprise 1 to 20 carbon atoms, 1-10 carbons or 1-6 carbons.
- [423] The term “a substituted hydrocarbyl” refers to a hydrocarbyl radical that is substituted with a group comprising at least one atom other than carbon, such as but not limited to, halogen, oxygen, nitrogen, sulfur and phosphorus. Examples of such substituted hydrocarbyl include hydrocarbyl radicals substituted with groups such as, but not limited to, lower alkoxy such as

methoxy, ethoxy, and butoxy; halogen such as chloro and fluoro; ethers; acetals; ketals; esters; heterocyclyl such as furyl and thienyl; alkanoxy; hydroxy; protected hydroxy; acyl; acyloxy; nitro; cyano; amino; and amido. Substituted hydrocarbyl also includes hydrocarbyl radicals in which a carbon chain atom is replaced with a heteroatom such as nitrogen, oxygen, sulfur, or a halogen.

- [424] The term “sugar protecting group” means a protecting group on one or more hydroxy groups of a given sugar. Examples of such “sugar protecting groups” include, but are not limited to, acetyl, trialkylsilyl, alkyl (e.g., methyl), alkoxy (e.g., methoxy, ethoxy), tetrahydropyranyl (THP), etc.
- [425] Abbreviations used herein have the following meanings:

TERM	DEFINITION
THF	tetrahydrofuran
PTC	phase transfer catalyst
Aliquat 336	methyltricaprylylammonium chloride
MCPBA	m-chloroperbenzoic acid
Celite	a brand of diatomaceous earth filtering aid
DMF	Dimethylformamide
DME	-ethylene glycol dimethyl ether
BOC	t-butoxycarbonyl group
Me	Methyl
Et	Ethyl
Bu	Butyl
EtOAc	Ethyl acetate
Et ₂ O	diethyl ether
CH ₂ Cl ₂	methylene chloride
MgSO ₄	magnesium sulfate
NaOH	sodium hydroxide
CH ₃ OH	Methanol
HCl	hydrochloric acid
NaCl	sodium chloride
NaH	sodium hydride
LAH	lithium aluminum hydride
LiOH	lithium hydroxide
Na ₂ SO ₃	sodium sulfite
NaHCO ₃	sodium bicarbonate
DMSO	Dimethylsulfoxide

TERM	DEFINITION
KOSiMe ₃	potassium trimethylsilanolate
PEG	polyethylene glycol
MS	Mass spectrometry
HRMS	high resolution mass spectrometry
ES	Electrospray
NMR	nuclear magnetic resonance spectroscopy
GC	gas chromatography
MPLC	medium pressure liquid chromatography
HPLC	high pressure liquid chromatography
RPHPLC	reverse phase high pressure liquid chromatography
RT	Room temperature
h or hr	hour(s)
Min	minute(s)

[426] Biological Evaluation

- [427] The inhibitor concentration of the compounds of the present invention is to be determined by the following assays. These assays are to be performed *in vitro* and in animal models.
- [428] In Vitro Assay of Compounds that Inhibit ASBT-Mediated Uptake of [14C]-Taurocholate (TC) in H14 Cells
- [429] Seed baby hamster kidney cells (BHK) transfected with the cDNA of human ASBT (H14 cells) in 96 well Top-Count tissue culture plates at 60,000 cells/well (run assays within 24 hours of seeding), 30,000 cells/well (run assays within 48 hours of seeding), and 10,000 cells/well (run assays within 72 hours of seeding).
- [430] On the day of assay, gently wash the cell monolayer once with 100 mL assay buffer (Dulbecco's Modified Eagle's medium with 4.5 g/L glucose plus 0.2% (w/v) fatty acid free bovine serum albumin ((FAF) BSA). To each well, add 50 mL of a two-fold concentrate of test compound in assay buffer along with 50 mL of 6 mM [¹⁴C]-taurocholate in assay buffer (final concentration of 3 mM [¹⁴C]-taurocholate). Incubate the cell culture plates for 2 hours at 37°C prior to gently washing each well twice with 100 mL 4°C Dulbecco's

phosphate-buffered saline (PBS) containing 0.2% (w/v) (FAF)BSA. Then gently wash wells once with 100 mL 4°C PBS without (FAF)BSA. To each 200 mL of liquid, add scintillation counting fluid. Heat seal the plates and shake for 30 minutes at room temperature prior to measuring the amount of radioactivity in each well on a Packard Top-Count instrument.

[431] In Vitro Assay of Compounds that Inhibit Uptake of [¹⁴C]-Alanine

[432] The alanine uptake assay is performed in an identical fashion to the taurocholate assay, except that labeled alanine is substituted for the labeled taurocholate.

[433] In Vivo Assay of Compounds that Inhibit Rat Ileal Uptake of [¹⁴C]-Taurocholate into Bile

[434] (See Une *et al.* "Metabolism of 3 α ,7 β -dihydroxy-7 β -methyl-5 β -cholanoic acid and 3 α ,7 β -dihydroxy-7 α -methyl-5 β -cholanoic acid in hamsters", *Biochimica et Biophysica Acta*, Vol. 833, pp. 196-202 (1985)).

[435] Anesthetize male wistar rats (200-300 g) with inactin @100 mg/kg. Cannulate bile ducts with a 10" length of PE10 tubing. Expose the small intestine and lay out on a gauze pad. Insert a canulae (1/8" luer lock, tapered female adapter) at 12 cm from the junction of the small intestine and the cecum. Cut a slit at 4 cm from this same junction (utilizing a 8 cm length of ileum). Use 20 mL of warm Dulbecco's phosphate buffered saline, pH 6.5 ("PBS") to flush out the intestine segment. Cannulate the distal opening with a 20 cm length of silicone tubing (0.02" I.D. x 0.037" O.D.). Hook up the proximal cannulae to a peristaltic pump and wash the intestine for 20 minutes with warm PBS at 0.25 ml/minute. Continuously monitor the temperature of the gut segment.

[436] At the start of the experiment, load 2.0 mL of control sample ([¹⁴C]-taurocholate @ 0.05 mi/mL with 5 mM cold taurocholate) into the gut segment with a 3 mL syringe and begin bile sample collection. Infuse control sample at a rate of 0.25 ml/minute for 21 minutes. Collect bile sample

fractions every 3 minutes for the first 27 minutes of the procedure. After the 21 minutes of sample infusion, wash out the ileal loop with 20 mL of warm PBS (using a 30 mL syringe), and then wash out the loop for 21 minutes with warm PBS at 0.25 ml/minutes. Initiate a second perfusion as described above but with test compound being administered as well (21 minutes administration followed by 21 minutes of wash out) and sample bile every 3 minutes for the first 27 minutes. If necessary, conduct a third perfusion as above that containing the control sample.

- [437] Measurement of Hepatic Cholesterol Concentration (HEPATIC CHOL)
- [438] Weigh liver tissue and homogenize in chloroform:methanol (2:1). After homogenization and centrifugation, separate the supernatant and dry under nitrogen. Dissolve the residue in isopropanol and measure the cholesterol content enzymatically, using a combination of cholesterol oxidase and peroxidase, as described by Allain, C. A., *et al.*, *Clin. Chem.* 20, 470 (1974).
- [439] Measurement of Hepatic HMG CoA-Reductase Activity (HMG COA)
- [440] Prepare Hepatic microsomes by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. Resuspend the final pelleted material in buffer and assay an aliquot for HMG CoA reductase activity by incubating for 60 minutes at 37° C in the presence of ¹⁴C-HMG-CoA (Dupont-NEN). Stop the reaction by adding 6N HCl followed by centrifugation. Separate an aliquot of the supernatant by thin-layer chromatography, and scrape off the plate the spot corresponding to the enzyme product. Extract and determine radioactivity by scintillation counting. (See Akerlund, J. and Bjorkhem, I., *J. Lipid Res.* 31, 2159(1990)).
- [441] Determination of Serum Cholesterol (SER.CHOL, HDL-CHOL, TGI and VLDL + LDL)
- [442] Measure total serum cholesterol (SER.CHOL) enzymatically using a commercial kit from Wako Fine Chemicals (Richmond, VA); Cholesterol

C11, Catalog No. 276-64909. Assay HDL cholesterol (HDL-CHOL) using this same kit after precipitation of VLDL and LDL with Sigma Chemical Co. HDL Cholesterol reagent, Catalog No. 352-3 (dextran sulfate method). Enzymatically assay total serum triglycerides (blanked) (TGI) with Sigma Chemical Co. GPO-Trinder, Catalog No. 337-B. Calculate VLDL and LDL (VLDL + LDL) cholesterol concentrations as the difference between total and HDL cholesterol.

- [443] Measurement of Hepatic Cholesterol 7 α -Hydroxylase Activity (7 α -OHase)
- [444] Prepare hepatic microsomes by homogenizing liver samples in a phosphate/sucrose buffer, followed by centrifugal separation. Resuspend the final pelleted material in buffer and assay an aliquot for cholesterol 7 α -hydroxylase activity by incubating for 5 minutes at 37° C in the presence of NADPH. Following extraction into petroleum ether, evaporate the organic solvent and dissolve the residue in acetonitrile/ methanol. Separate the enzymatic product by injecting an aliquot of the extract onto a C₁₈ reversed phase HPLC column and quantitate the eluted material using UV detection at 240 nm. (See Horton, J. D., *et al.*, *J. Clin. Invest.* 93, 2084(1994).)
- [445] Rat Gavage Assay
- [446] Administer ASBT inhibitors to male Wister rats (275-300 g) using an oral gavage procedure. Administer drug or vehicle (0.2% Tween 80 in water) once a day (9:00-10:00 a.m.) for 4 days at varying dosages in a final volume of 2 mL per kilogram of body weight. Collect total fecal samples during the final 48 hours of the treatment period and analyze for bile acid content using an enzymatic assay as described below. Determine compound efficacy by comparison of the increase in fecal bile acid (FBA) concentration in treated rats to the mean FBA concentration of rats in the vehicle group.

[447] Measurement of Fecal Bile Acid Concentration (FBA)

[448] Collect total fecal output from individually housed hamsters is collected for 24 or 48 hours, dried under a stream of nitrogen, pulverized and weighed. Approximately 0.1 gram is weighed out and extracted into an organic solvent (butanol/water). Following separation and drying, the residue is dissolved in methanol and the amount of bile acid present is measured enzymatically using the 3 α -hydroxysteroid steroid dehydrogenase reaction with bile acids to reduce NAD. (See Mashige, F., *et al.*, *Clin. Chem.* 27, 1352 (1981)).

[449] [3 H]taurocholate Uptake in Rabbit Brush Border Membrane Vesicles (BBMV)

[450] Prepare rabbit ileal brush border membranes from frozen ileal mucosa by the calcium precipitation method described by Malathi *et al.* (See *Biochimica Biophysica Acta*, 554, 259 (1979)). The method for measuring taurocholate is essentially as described by Kramer *et al.* (Reference: (1992) *Biochimica Biophysica Acta*, 1111, 93) except the assay volume is 200 μ L instead of 100 μ L. Briefly, incubate at room temperature a 190 μ L solution containing 2 μ M [3 H]-taurocholate (0.75 μ Ci), 20 mM tris, 100 mM sodium chloride, 100 mM mannitol pH 7.4 for 5 seconds with 10 μ L of brush border membrane vesicles (60-120 μ g protein). Initiate the incubation by the addition of BBMV while vortexing and stop the reaction by the addition of 5 mL of ice cold buffer (20 mM Hepes-tris, 150 mM KCl) followed immediately by filtration through a nylon filter (0.2 μ m pore) and an additional 5 mL wash with stop buffer.

[451] Acyl-CoA; Cholesterol Acyl Transferase (ACAT)

[452] Prepare hamster liver and rat intestinal microsomes from tissue as described previously (See *J. Biol. Chem.* 255, 9098 (1980)) and use as a source of ACAT enzyme. The assay consists of a 2.0 mL incubation containing 24 μ M Oleoyl-CoA (0.05 μ Ci) in a 50 mM sodium phosphate, 2 mM DTT pH 7.4 buffer containing 0.25 % BSA and 200 μ g of microsomal protein. Initiate the assay by the addition of oleoyl-CoA. Allow the reaction to proceed for 5 minutes at 37°C and terminate it by the addition of 8.0 mL of chloroform/

methanol (2:1). To the extraction, add 125 µg of cholesterol oleate in chloroform methanol to act as a carrier and the organic and separate the aqueous phases of the extraction by centrifugation after thorough vortexing. Take the chloroform phase to dryness and then spot on a silica gel 60 thin layer chromatography plate and develop in hexane/ethyl ether (9:1). Determine the amount of cholesterol ester formed by measuring the amount of radioactivity incorporated into the cholesterol oleate spot on the thin layer chromatography plate with a Packard instaimager.

[453] As various changes could be made in the above methods and apparatus without departing from the scope of the invention, it is intended that all matter contained in the above description be interpreted as illustrative and not in a limiting sense. All documents, books, patents, references and publications mentioned in this application are expressly incorporated by reference in their entirety as if fully set forth at length.

[454] Dog Model for the Evaluation of Lipid-Lowering Drugs

[455] Obtain male beagle dogs weighing 6-12 kg from a vendor, such as Marshall farms. Feed each dog once a day for two hours and give water ad libitum. Randomly assign dogs to dosing groups consisting of 6 to 12 dogs each, corresponding to: vehicle, i.g.; 1 mg/kg, i.g.; 2 mg/kg, i.g.; 4 mg/kg, i.g.; 2 mg/kg, p.o. (powder in capsule). Perform intra-gastric dosing of a therapeutic compound dissolved in aqueous solution (for example, 0.2% Tween 80 solution (polyoxyethylene mono-oleate, Sigma Chemical Co., St. Louis, MO)) using a gavage tube. Prior to initiating dosing, draw blood samples from the cephalic vein before the morning feeding in order to evaluate serum cholesterol (total and HDL) and triglycerides. For several consecutive days, dose animals in the morning prior to feeding. Thereafter, allow animals to eat for two hours before remaining food is removed. Collect feces over a 2-day period at the end of the study and analyze for bile acid or lipid content. Collect blood samples at the end of the treatment period for comparison with

pre-study serum lipid levels. Determine statistical significance using the standard Student's T-test, with $p < .05$.

[456] Dog Serum Lipid Measurement

- [457] Collect blood from the cephalic veins of fasted dogs using serum separator tubes (Vacutainer SST, Becton Dickinson and Co., Franklin Lakes, NJ). Centrifuge the blood at 2000 rpm for 20 minutes and decant the serum.
- [458] Measure total cholesterol in a 96-well format using a Wako enzymatic diagnostic kit (Cholesterol CII) (Wako Chemicals, Richmond, VA), utilizing the cholesterol oxidase reaction to produce hydrogen peroxide, which is measured colorimetrically. Prepare a standard curve from 0.5 to 10 mg cholesterol in the first two columns of the plate. Add the serum samples (20-40 mL, depending on the expected lipid concentration) or known serum control samples to individual wells in duplicate. Add water to bring the volume to 100 mL in each well. Add a 100-mL aliquot of color reagent to each well, and read the plates at 500 nm after a 15-minute incubation at 37°C.
- [459] HDL cholesterol was assayed using Sigma kit No. 352-3 (Sigma Chemical Co., St. Louis, MO), which utilizes dextran sulfate and Mg^{2+} to selectively precipitate LDL and VLDL. Add a volume of 150 mL of each serum sample to individual microfuge tubes, followed by 15 mL of HDL cholesterol reagent (Sigma 352-3). Mix samples and centrifuge at 5000 rpm for 5 minutes. Then mix a 50 mL aliquot of the supernatant with 200 mL of saline and assay using the same procedure as for total cholesterol measurement.
- [460] Measure triglycerides using Sigma kit No. 337 in a 96-well plate format. This procedure will measure the release glycerol from triglycerides with lipoprotein lipase. Use standard solutions of glycerol (Sigma 339-11) ranging from 1 to 24 mg to generate the standard curve. Add serum samples (20-40 mL, depending on the expected lipid concentration) to wells in duplicate. Add water to bring the volume to 100 mL in each well and then add 100 mL of color reagent to each well. After mixing and a 15-minutes of incubation, read

the plates at 540 nm and calculate the triglyceride values from the standard curve. Run a replicate plate using a blank enzyme reagent to correct for any endogenous glycerol in the serum samples.

[461] Dog Fecal Bile Acid Measurement

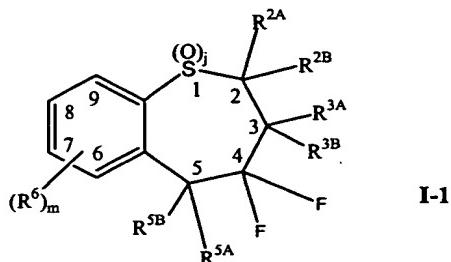
- [462] Collect fecal samples to determine the fecal bile acid (FBA) concentration for each animal. Obtain fecal collections during the final 48 hours of the study, for two consecutive 24-hour periods between 9:00 a.m. and 10:00 a.m. each day, prior to dosing and feeding. Weigh the separate two-day collections from each animal, combine and homogenize with distilled water in a processor (Cuisinart) to generate a homogeneous slurry. Extract a sample of 1.4 g of the homogenate in a final concentration of 50% tertiary butanol/distilled water (2:0.6) for 45 minutes in a 37°C water bath and centrifuge for 13 minutes at 2000 x G.
- [463] Determine the concentration of bile acids (mmoles/day) using a 96-well enzymatic assay system. Add a 20-mL aliquot of the fecal extract to two sets each of triplicate wells in a 96-well assay plate. Analyze a standardized sodium taurocholate solution and a standardized fecal extract solution (previously made from pooled samples and characterized for its bile acid concentration) for assay quality control. Similarly add aliquots of sodium taurocholate (20 mL), serially diluted to generate a standard curve, to two sets of triplicate wells. Add a 230-mL reaction mixture containing 1M hydrazine hydrate, 0.1 M pyrophosphate and 0.46 mg/ml NAD to each well. Then add a 50- mL aliquot of 3 α -hydroxysteroid dehydrogenase enzyme (HSD; 0.8 units/ml) or assay buffer (0.1 M sodium pyrophosphate) to one of the two sets of triplicates. Obtain all reagents from Sigma Chemical Co., St. Louis, MO. Following 60 minutes of incubation at room temperature, measure the optical density at 340 nm and calculate the mean of each set of triplicate samples. Use the difference in optical density \pm HSD enzyme to determine the bile acid concentration (mM) of each sample, based on the sodium taurocholate standard curve. Use the bile acid concentration of the extract, the weight of

the fecal homogenate (grams) and the body weight of the animal to calculate the corresponding FBA concentration in mmoles/kg/day for each animal. Subtract the mean FBA concentration (mmoles/kg/day) of the vehicle group from the FBA concentration of each treatment group to determine the increase (delta value) in FBA concentration as a result of the treatment.

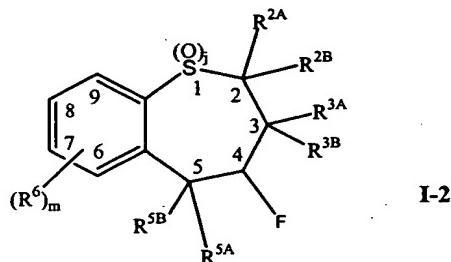
- [464] Below are various illustrative examples for making various compounds in connection with the invention. The following examples and specific embodiments are provided for illustrative purposes and not intended to limit the scope of the invention.

SPECIFIC EMBODIMENTS

[465] 1. A compound comprising a benzothiepene of Formula I-1 or I-2:



or



or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A}, R^{3B}, R^{5A}, and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl-R⁵; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R⁵ is selected from the group consisting of hydrogen; hydrocarbyl, heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein when R⁵ is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with -NH-X-R or -O-X-R;

wherein X is selected from the group consisting of -(C=O)_s-alkyl-; -(C=O)_s-alkyl-NH-; -(C=O)_s-alkyl-O-; -(C=O)_s-alkyl-(C=O); and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R⁹ and R¹⁰ are as previously defined;

wherein, when R⁵ ≠ H, R⁵ is optionally substituted with one or more radicals independently selected from the group consisting of halogen; -NO₂; -CN; oxo; hydrocarbyl; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻;

wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A⁻ is a pharmaceutically acceptable anion;

wherein M is a pharmaceutically acceptable cation;

wherein one or more R⁶ radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

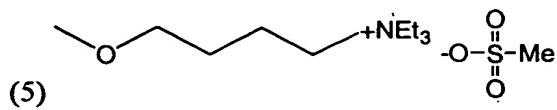
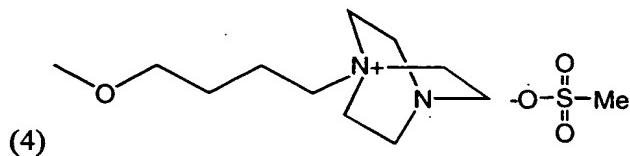
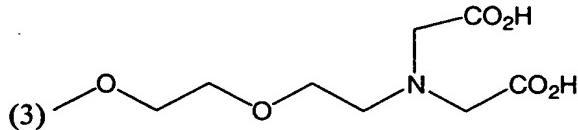
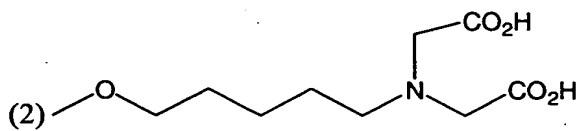
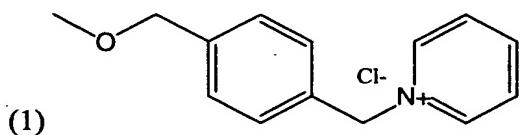
wherein R¹³, R¹⁴, R¹⁵, A⁻, and M are as defined above; and

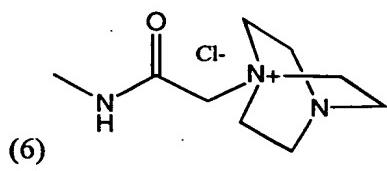
wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms

replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.

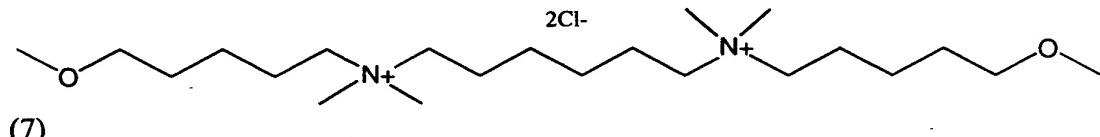
[466] 2. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and alkyl, R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl and arakyl and R⁵ is selected from the group consisting of alkyl, cycloalkyl, alkenyl, alkynyl and aryl.

[467] 3. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{5A} is aryl optionally substituted with said radical R⁵ selected from the group consisting of (1) - (69) and (70):

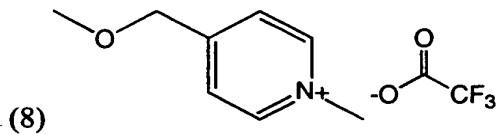




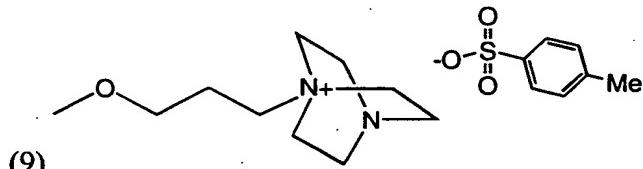
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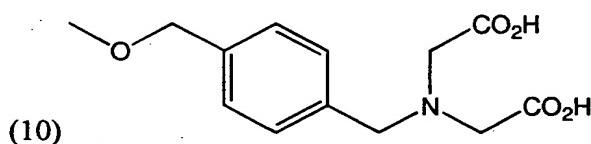
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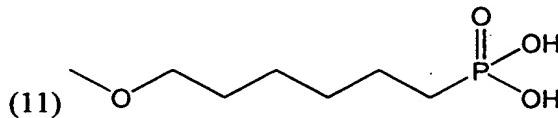
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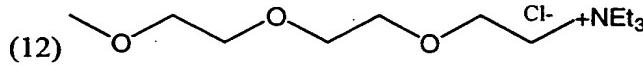
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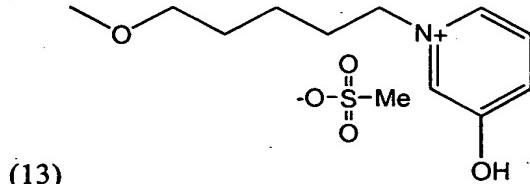
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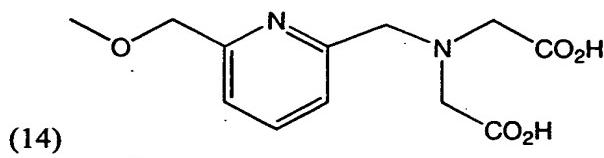
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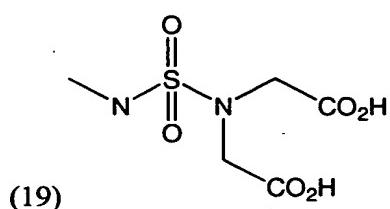
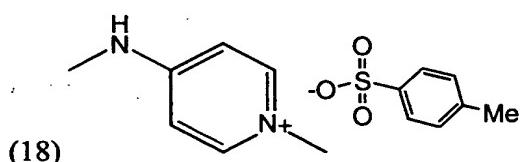
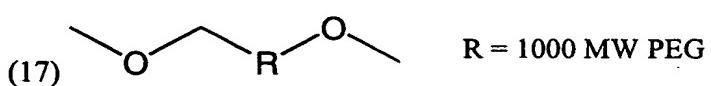
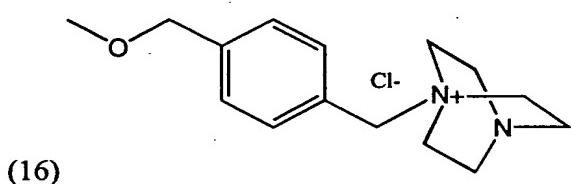
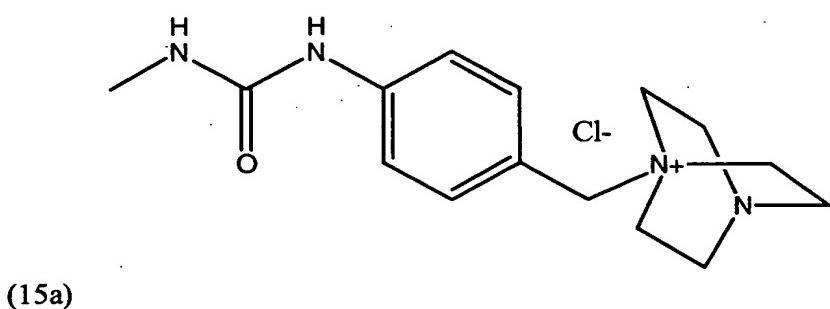
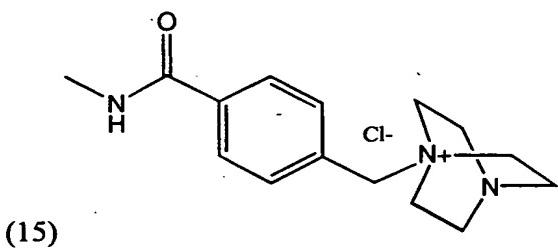
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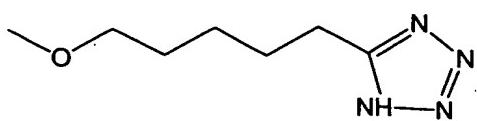


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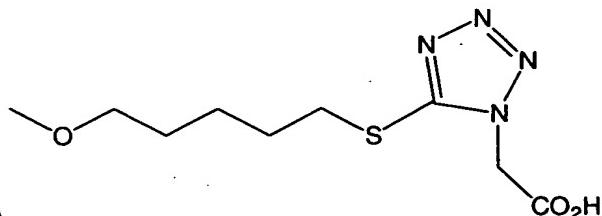


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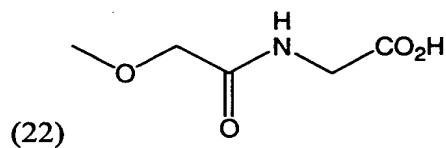




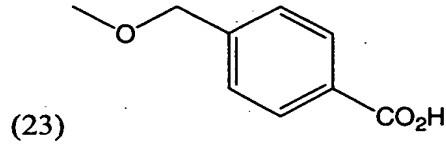
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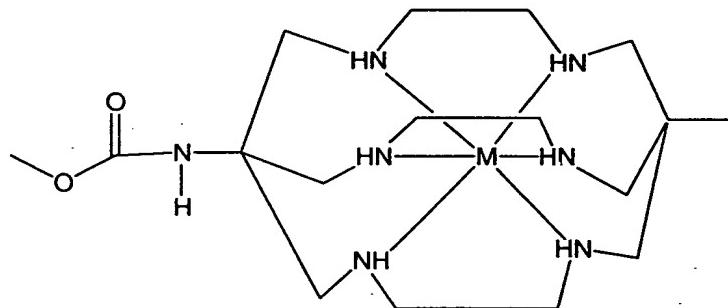
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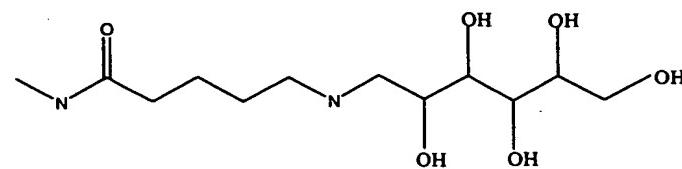
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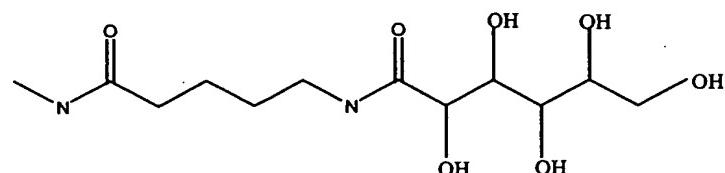
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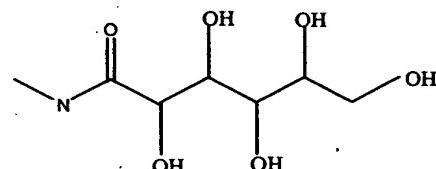
(24) $\text{M} = \text{Co}^{\text{II}}, ^{\text{III}}$, $\text{Mn}^{\text{II}}, ^{\text{III}}$, $\text{Fe}^{\text{II}}, ^{\text{III}}$, $\text{Ni}^{\text{II}}, ^{\text{III}}$,
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 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}



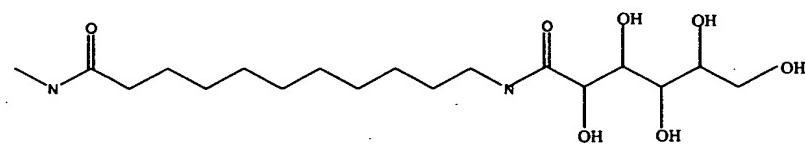
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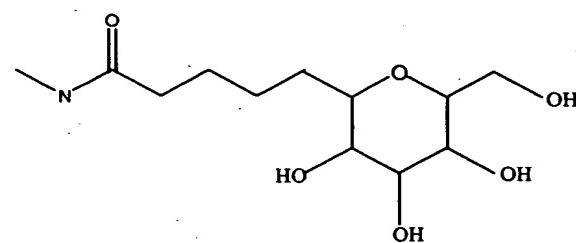
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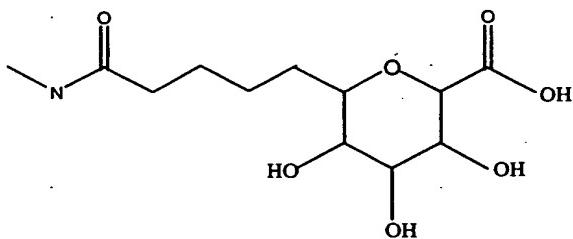
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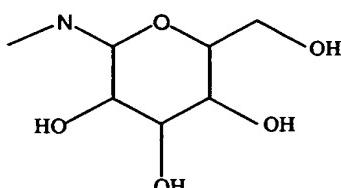
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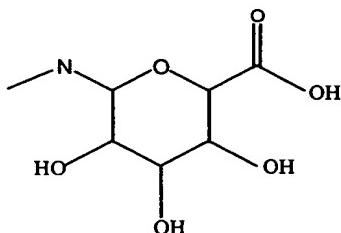
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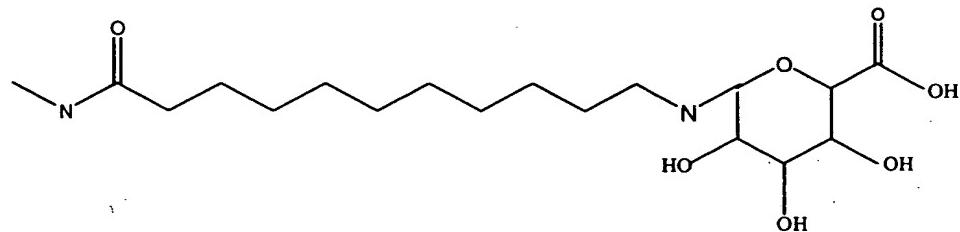
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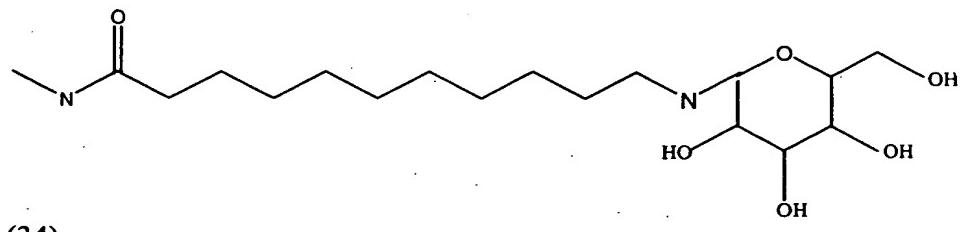
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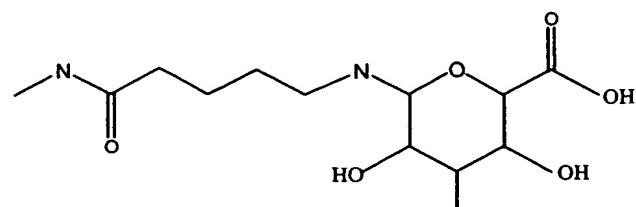
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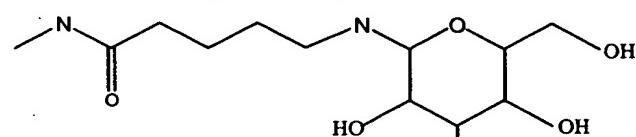
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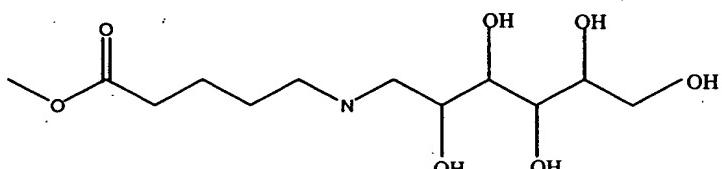
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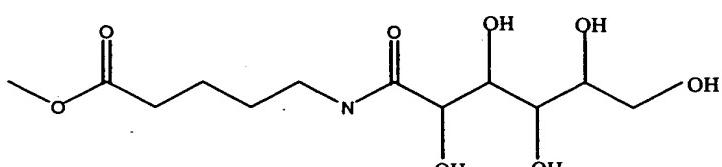
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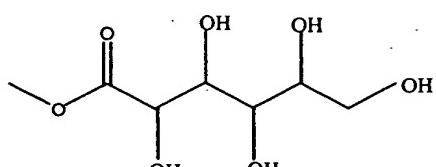
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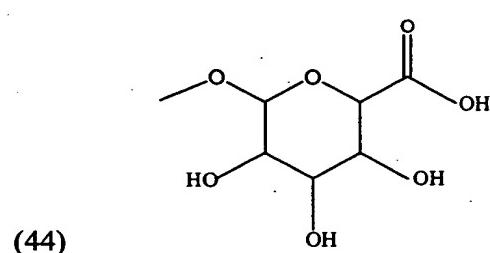
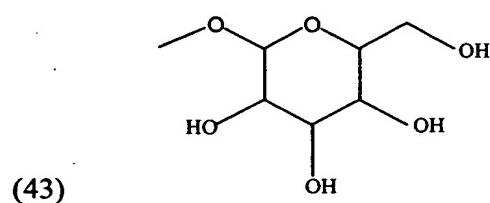
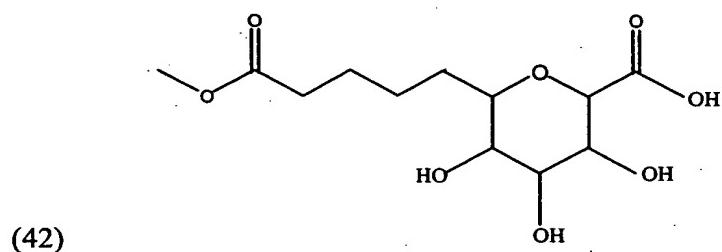
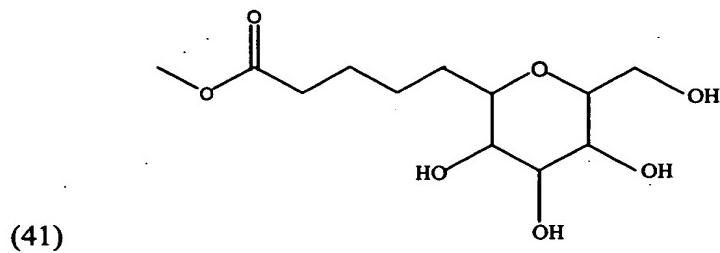
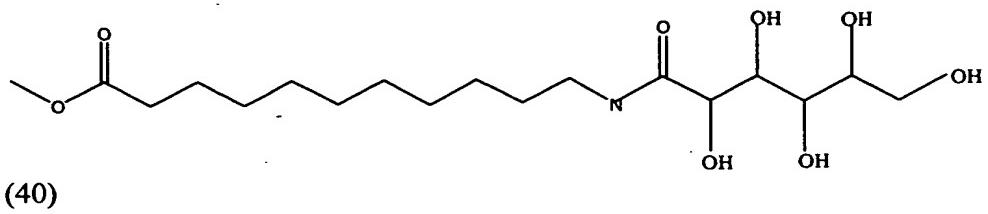
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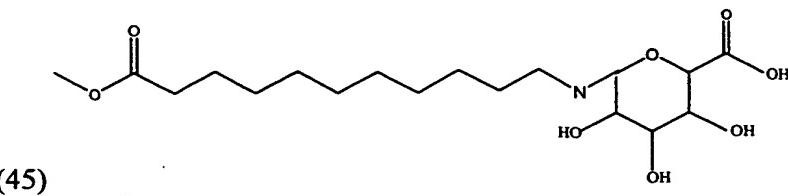


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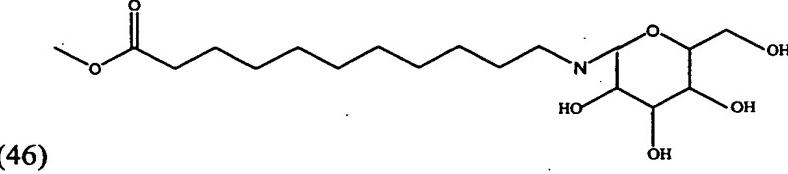


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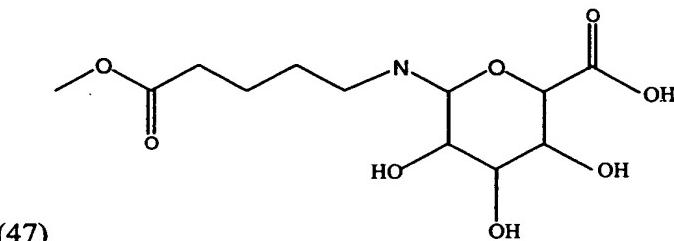




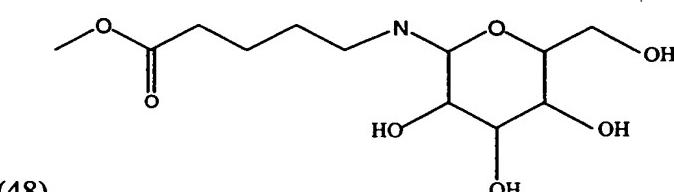
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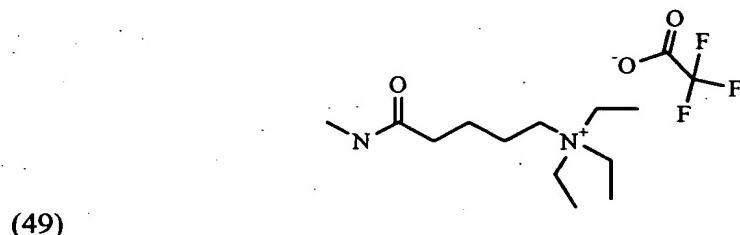
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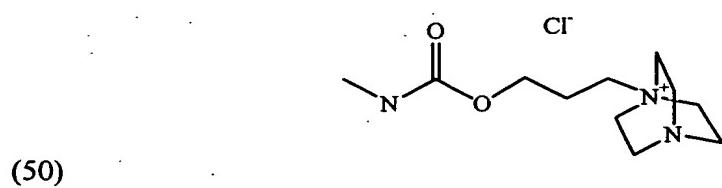
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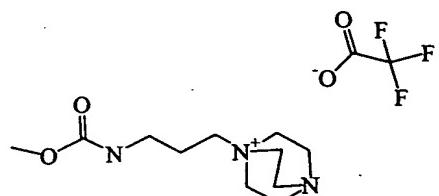
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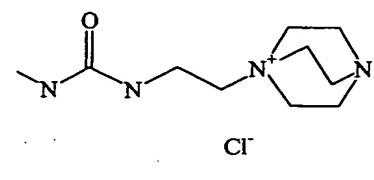
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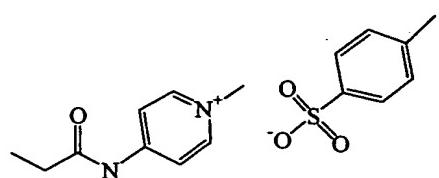
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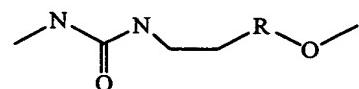
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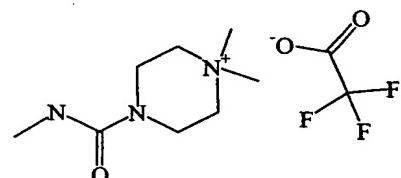
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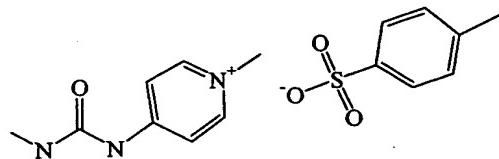
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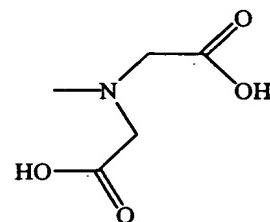
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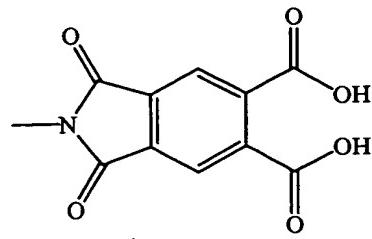
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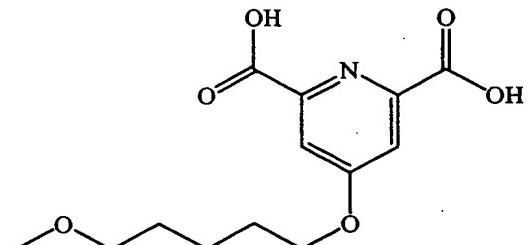
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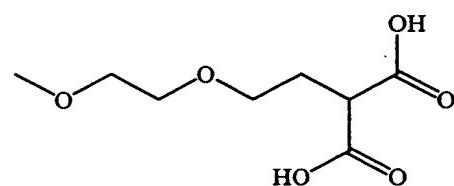
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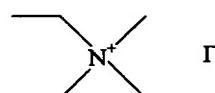
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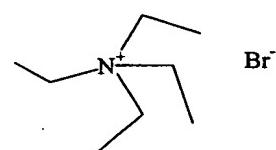
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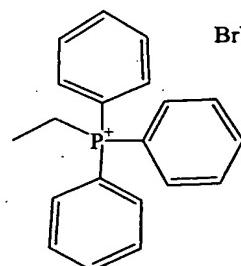
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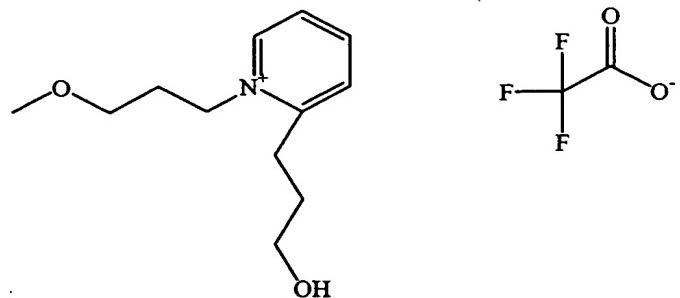
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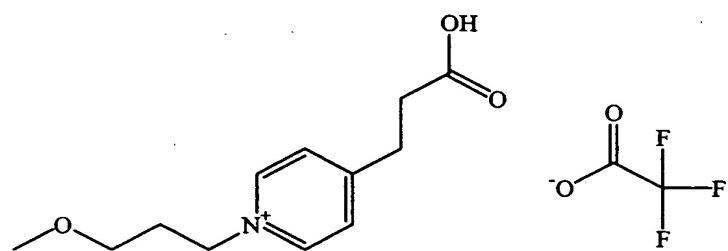
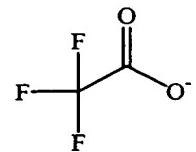
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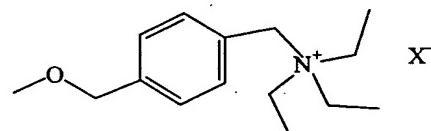
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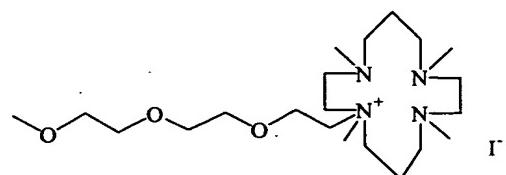
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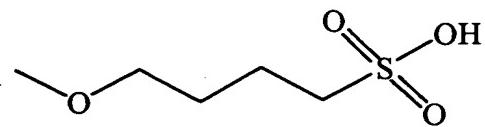


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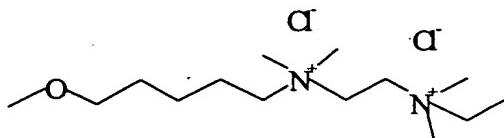


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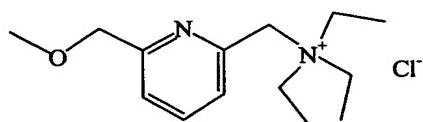
(68)



(69) and



(70)



provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and R^{5B} is a right end of said R⁵ or vice versa.

[468] 4. The compound of embodiment 3 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{5A} is phenyl optionally substituted at least at either a para position or a meta position of said phenyl with said radical R⁵.

[469] 5. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein j = 2, R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and alkyl, and R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen and alkyl.

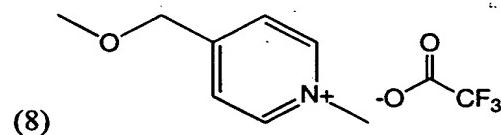
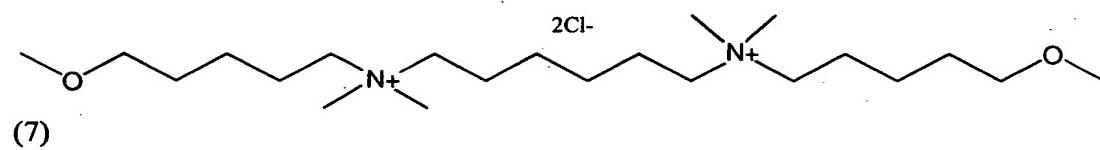
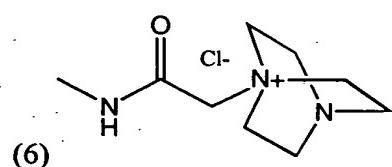
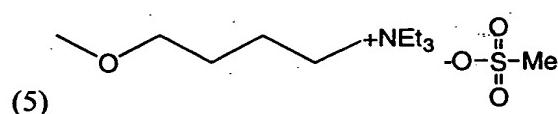
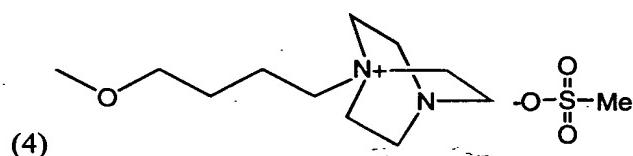
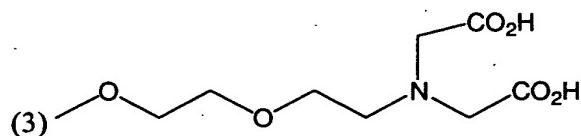
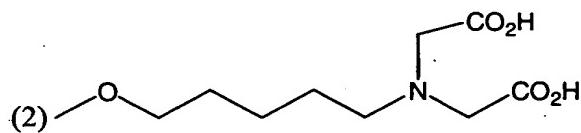
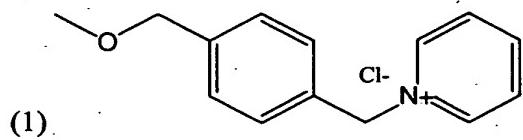
- [470] 6. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein $j = 2$, at least one of R^{2A} and R^{2B} is hydrogen, and R^{3A} and R^{3B} each are alkyl.
- [471] 7. The compound of embodiment 6 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein $R^{2A} = R^{2B} = H$ and R^{3A} and R^{3B} are independently selected from the group consisting of ethyl, propyl and butyl.
- [472] 8. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and C_{1-10} alkyl, R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen and C_{1-10} alkyl.
- [473] 9. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl, and R^{3A} and R^{3B} are independently selected from the group consisting of hydrogen and C_{1-6} alkyl.
- [474] 10. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same radical.
- [475] 11. The compound of embodiment 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same alkyl radical.

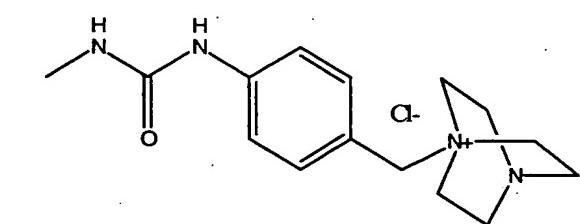
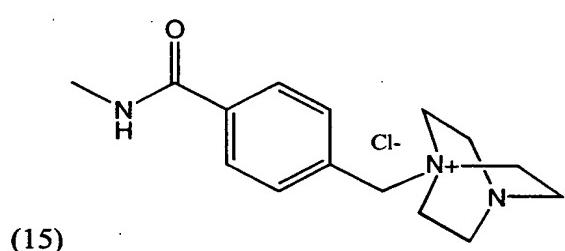
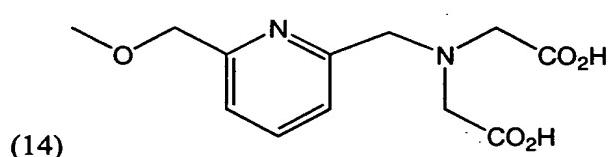
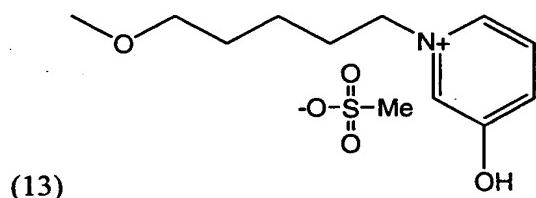
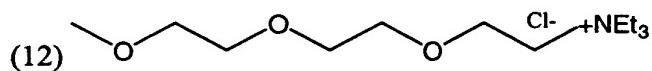
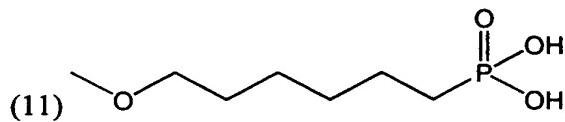
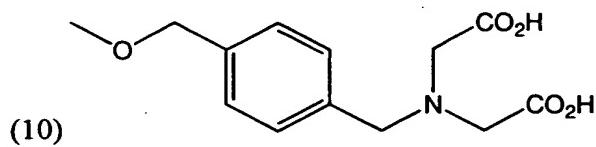
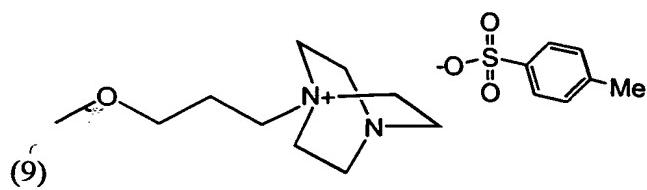
- [476] 12. The compound of embodiment 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same radical selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkenyl and C₁₋₁₀ alkynyl.
- [477] 13. The compound of embodiment 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same radical.
- [478] 14. The compound of embodiment 11 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same alkyl radical.
- [479] 15. The compound of embodiment 12 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same radical selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkenyl and C₁₋₁₀ alkynyl.
- [480] 16. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same radical.
- [481] 17. The compound of embodiment 16 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same alkyl radical.

- [482] 18. The compound of embodiment 16 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same radical selected from the group consisting of hydrogen, C₁₋₁₀ alkyl, C₁₋₁₀ alkenyl and C₁₋₁₀ alkynyl.
- [483] 19. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same C₁₋₂₀ hydrocarbyl radical.
- [484] 20. The compound of embodiment 19 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same C₁₋₁₀ hydrocarbyl radical.
- [485] 21. The compound of embodiment 20 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are the same C₁₋₆ hydrocarbyl radical.
- [486] 22. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same C₁₋₂₀ hydrocarbyl radical.
- [487] 23. The compound of embodiment 22 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same C₁₋₁₀ hydrocarbyl radical.

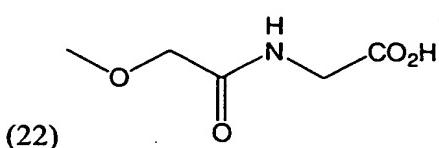
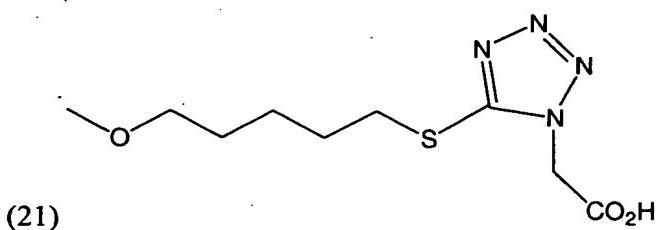
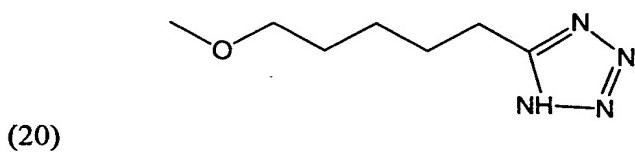
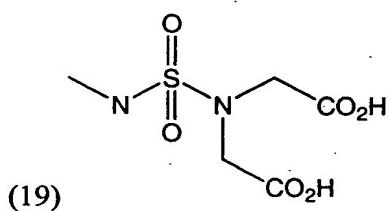
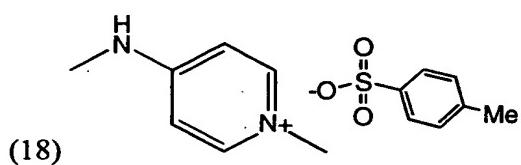
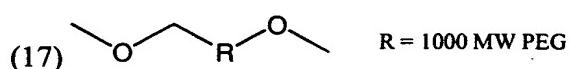
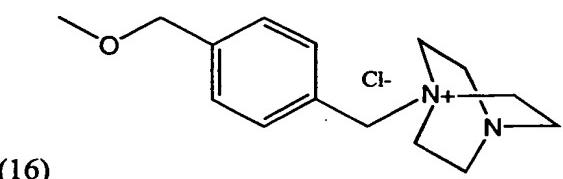
- [488] 24. The compound of embodiment 23 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are the same C₁₋₆ hydrocarbyl radical.
- [489] 25. The compound of embodiment 11 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are each n-butyl.
- [490] 26. The compound of embodiment 10 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{2A} and R^{2B} are each H.
- [491] 27. The compound of embodiment 13 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein R^{3A} and R^{3B} are each H or n-butyl.
- [492] 28. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein one or more radicals R⁶ are selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, amino, alkylamino and dialkylamino.
- [493] 29. The compound of embodiment 28 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein one or more radicals R⁶ are selected from the group consisting of methoxy, ethoxy and dimethylamino.

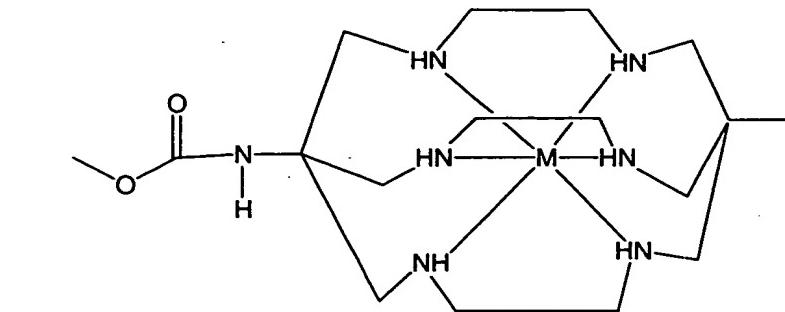
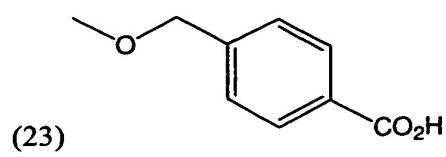
[494] 30. The compound of embodiment 1 or a pharmaceutically acceptable salt, solvate or prodrug thereof, wherein $j = 2$, $m = 1$, one of R^{5A} and R^{5B} is hydrogen and the other of R^{5A} and R^{5B} is a phenyl radical optionally substituted at a para position of said phenyl radical with said radical R^5 selected from the group consisting of (1) - (69) and (70):





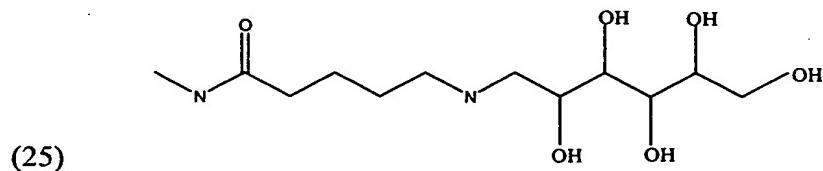
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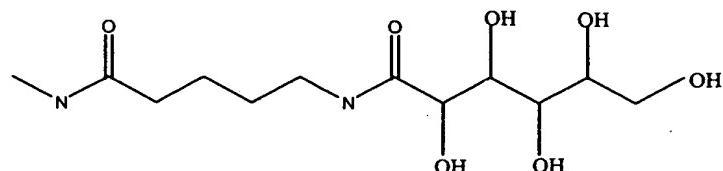


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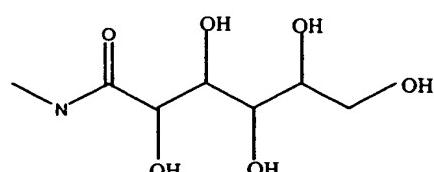
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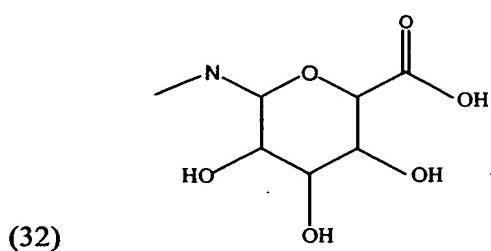
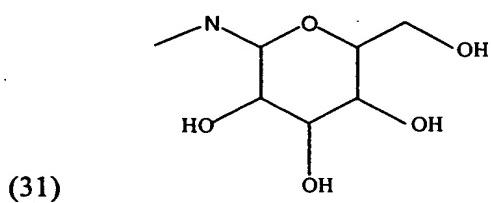
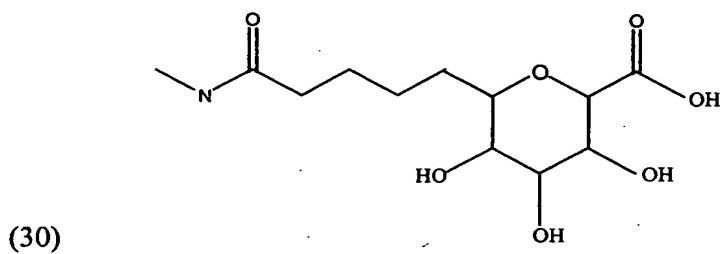
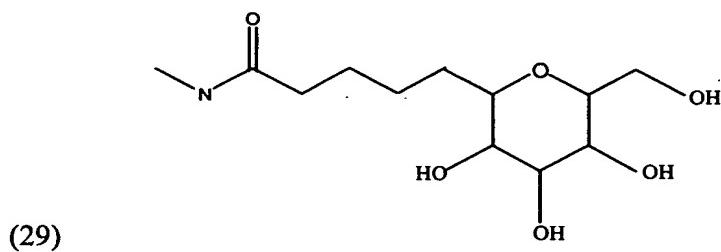
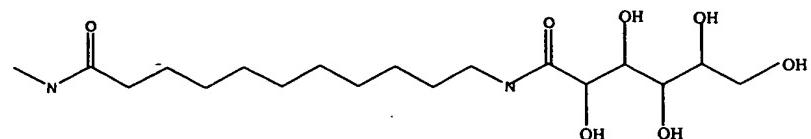


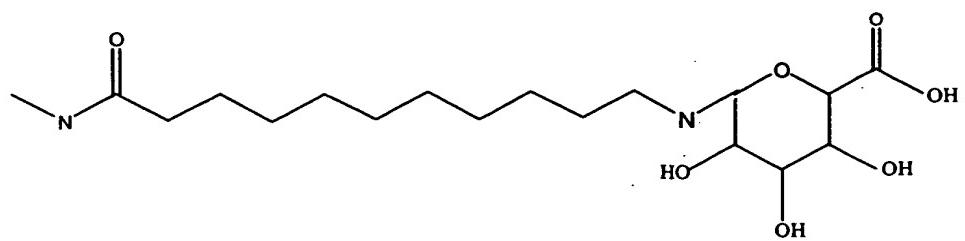
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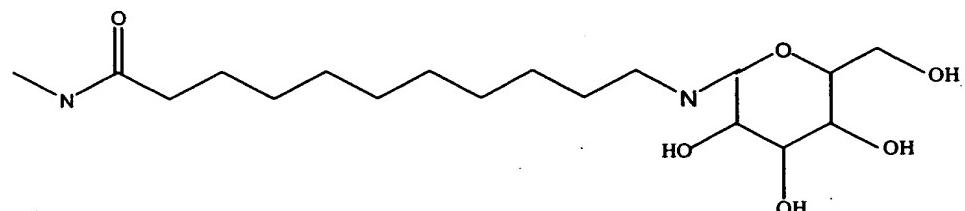
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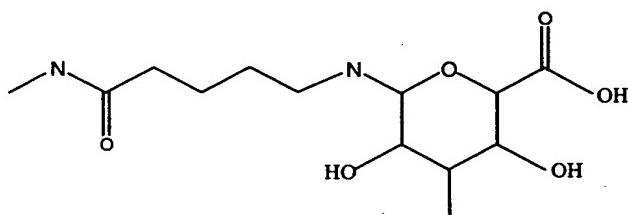




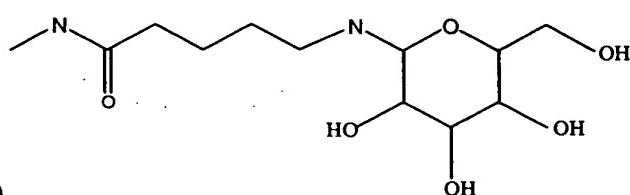
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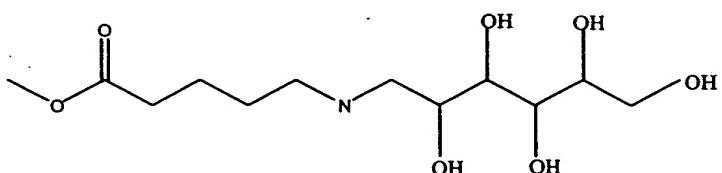
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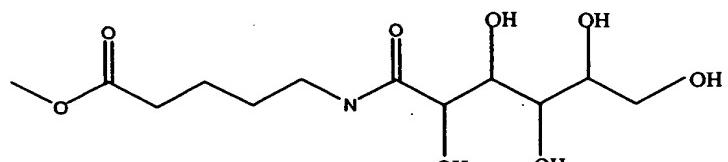
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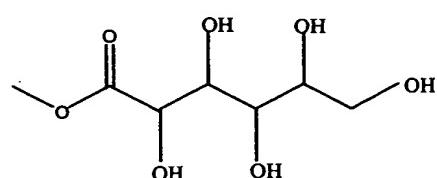
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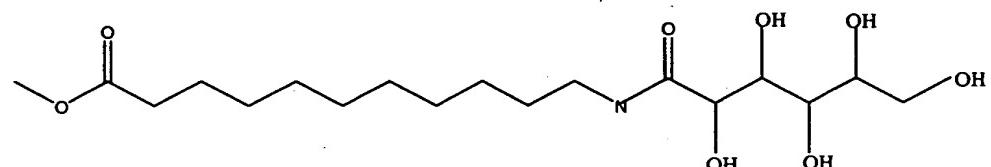
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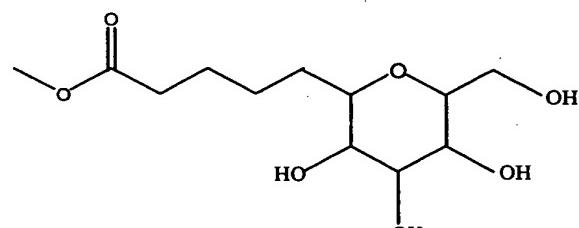
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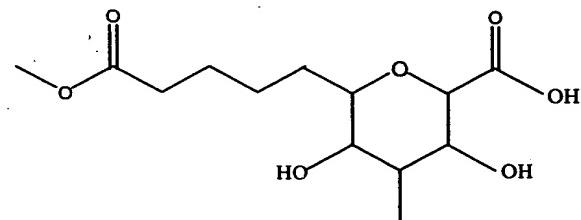
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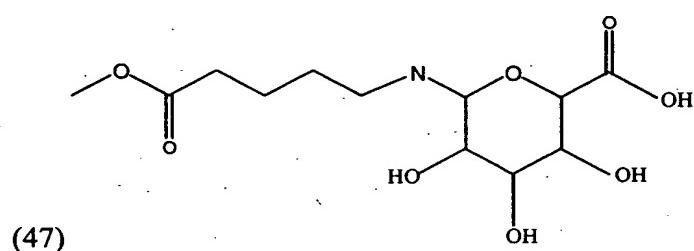
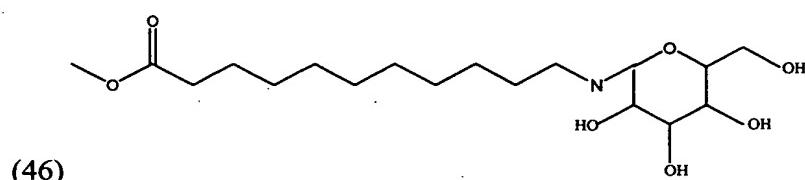
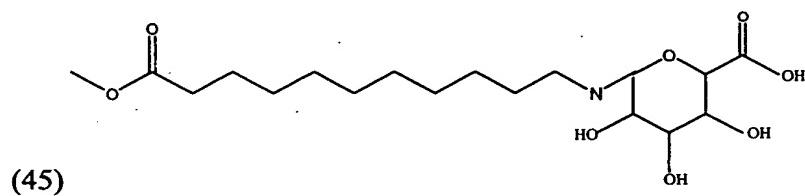
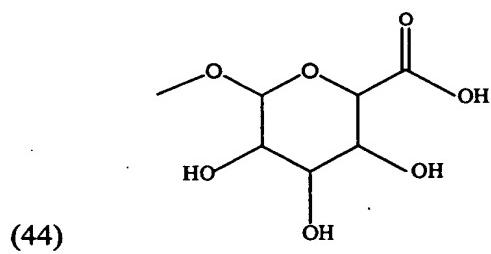
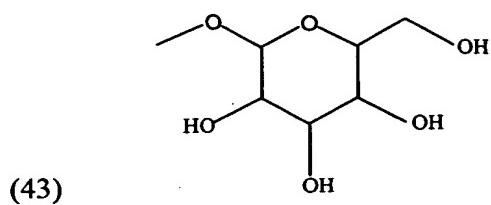
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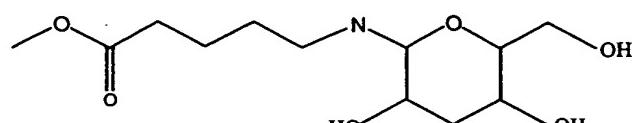


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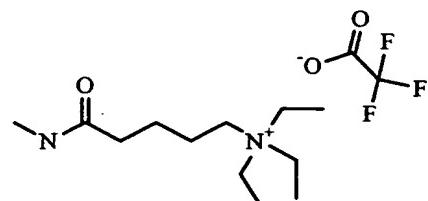


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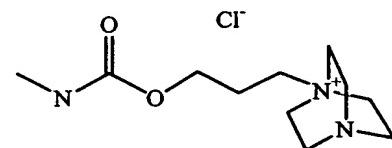




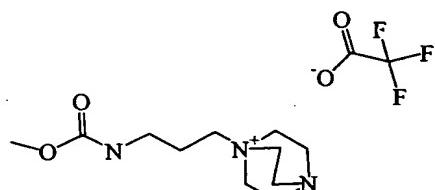
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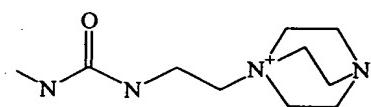
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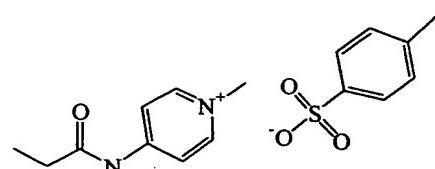
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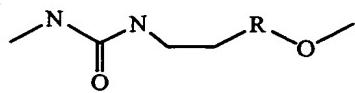
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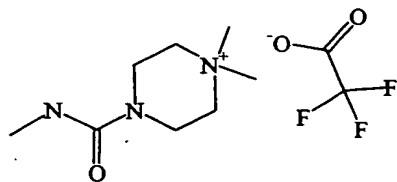
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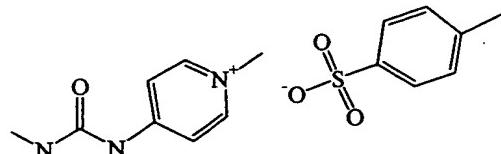
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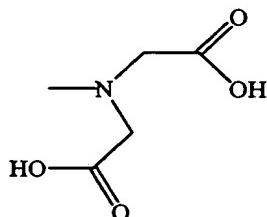
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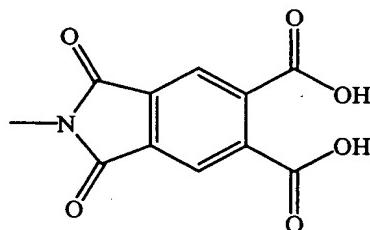
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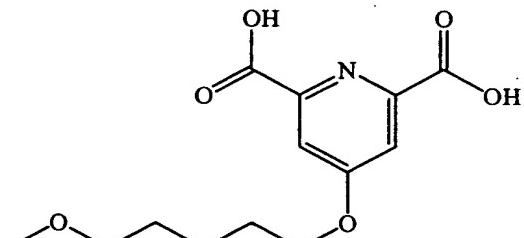
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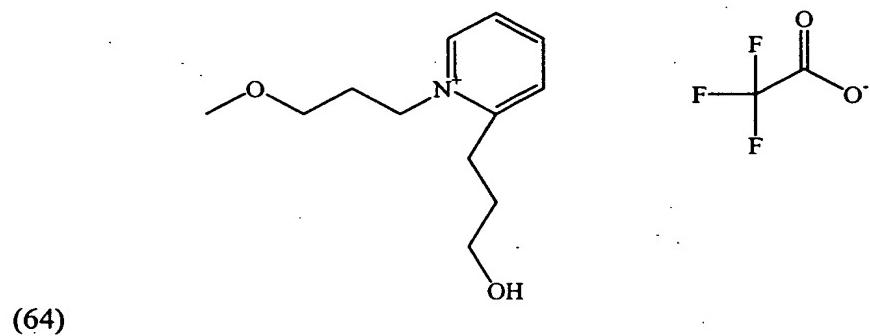
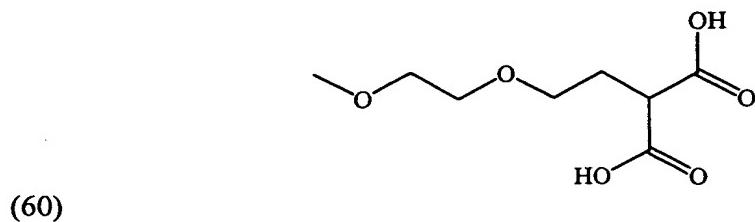
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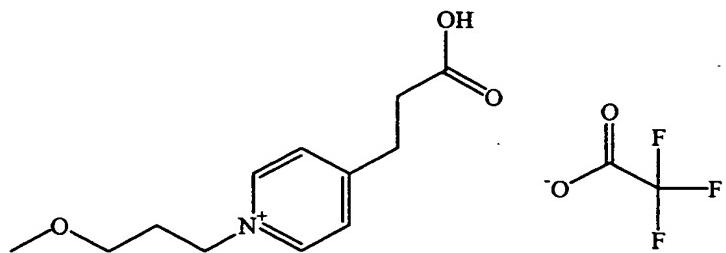


(58)



(59)





(65)

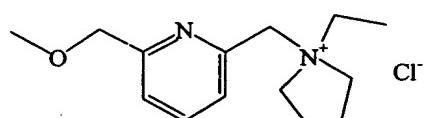
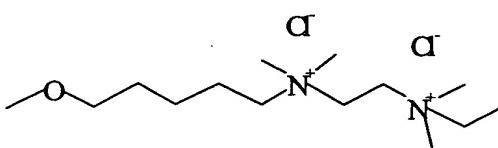
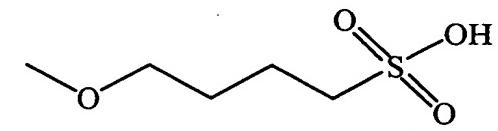
(66)

(67)

(68)

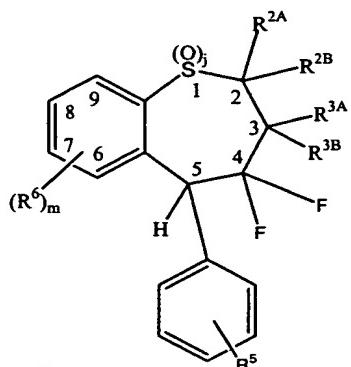
(69) and

(70)

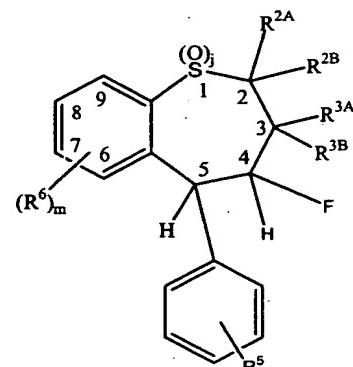


provided that when said R^5 is (7), (17) or (24), then said R^{5A} is a left end of said R^5 and R^{5B} is a right end of said R^5 or vice versa.

- [495] 31. The compound of embodiment 1 wherein said benzothiepene comprises the compound of Formula I-17 or I-18:



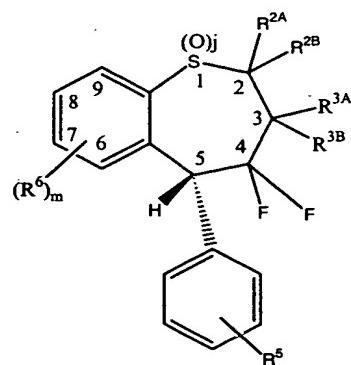
I-17



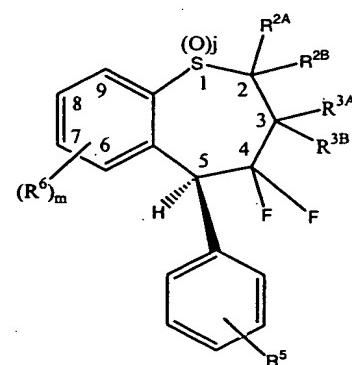
I-18.

- [496] 32. The compound of embodiment 31 wherein said R^5 is attached to either a para-position or a meta-position on said phenyl ring attached to the 5-position ring carbon of said benzothiepene compound of said Formulas I-17 or I-18.

- [497] 33. The compound of embodiment 31 wherein said benzothiepene of said Formula I-17 comprises a member selected from the group consisting



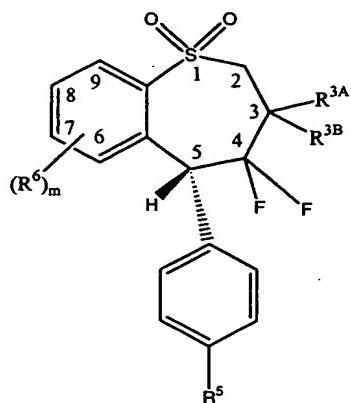
I-21



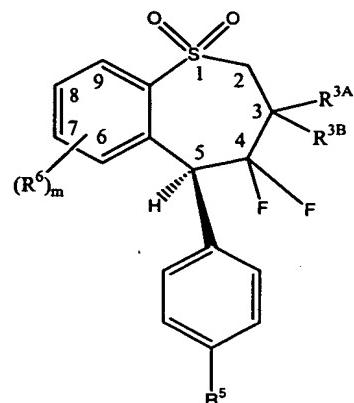
I-22.

of Formulas I-21 and I-22:

[498] 34. The compound of embodiment 33 wherein said benzothiepene of said Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:

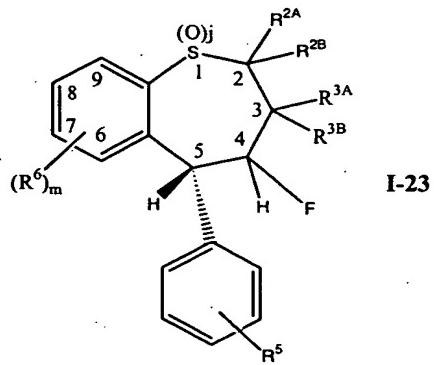


I-9

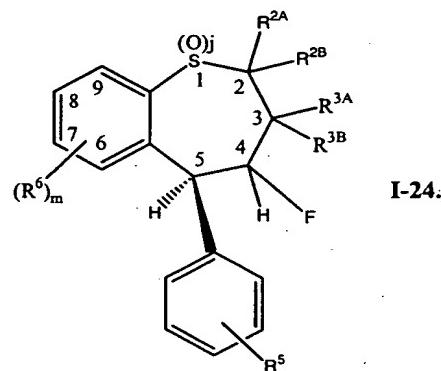


I-10.

[499] 35. The compound of embodiment 31 wherein said benzothiepene of said Formula I-18 comprises a member selected from the group consisting of Formulas I-23, and I-24:

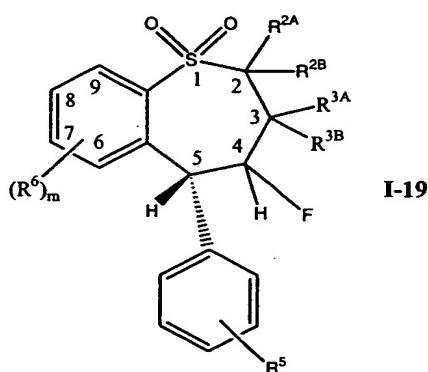


I-23

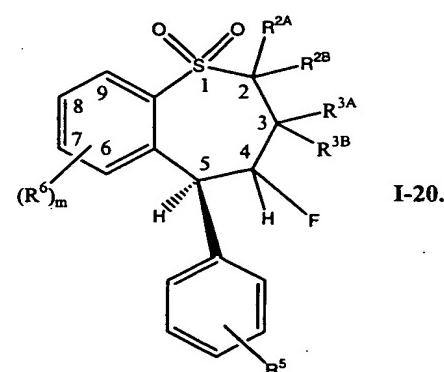


I-24.

[500] 36. The compound of embodiment 35 wherein said benzothiepene of said Formulas I-23 and I-24 comprise Formulas I-19 and I-20, respectively, represented by:



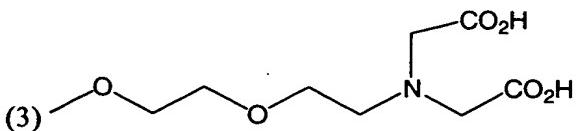
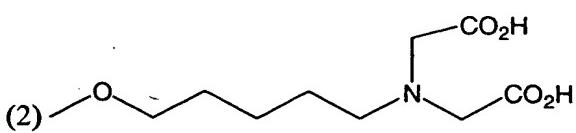
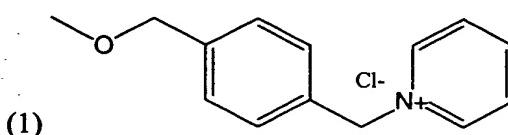
I-19

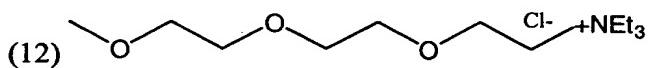
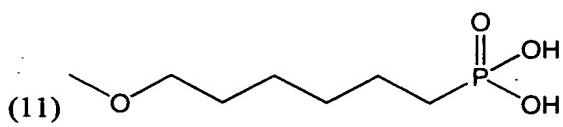
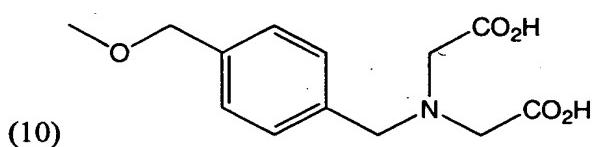
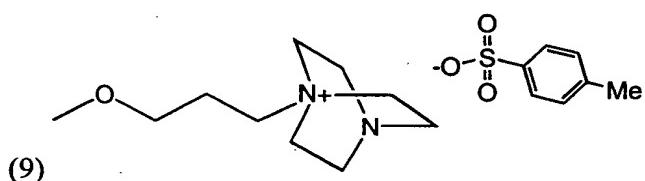
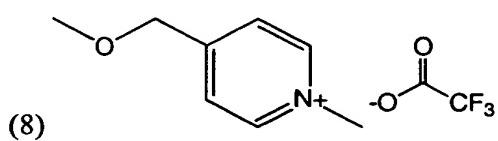
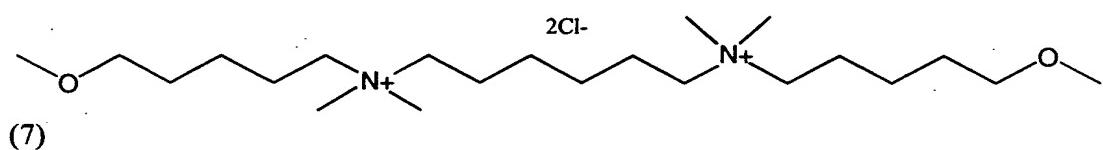
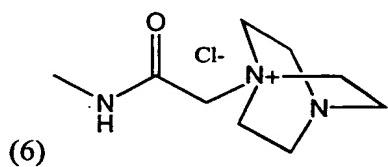
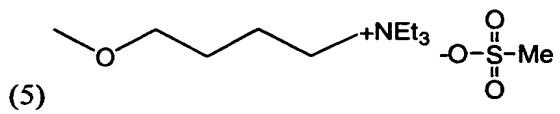
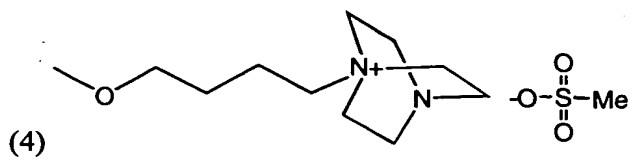


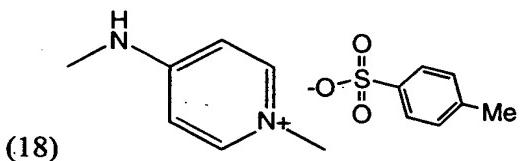
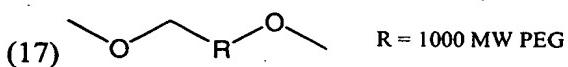
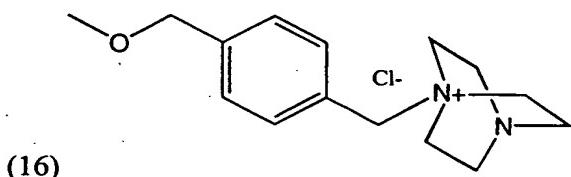
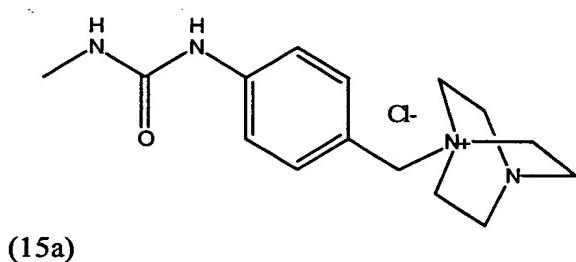
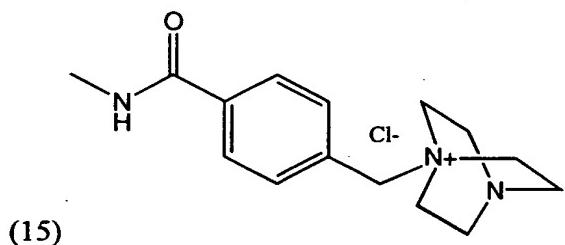
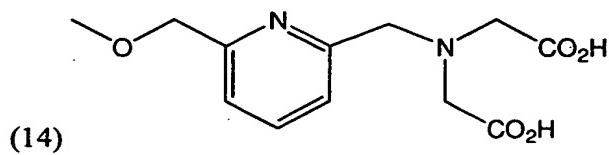
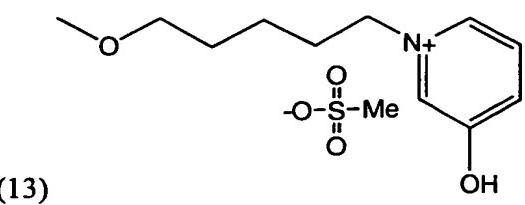
I-20.

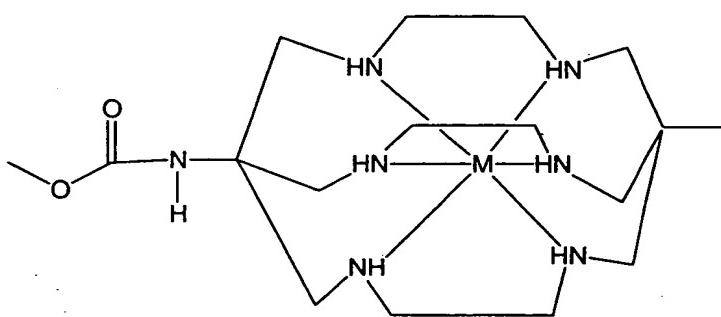
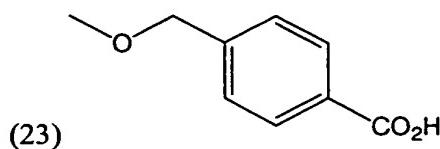
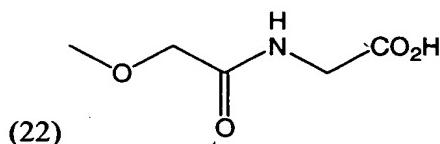
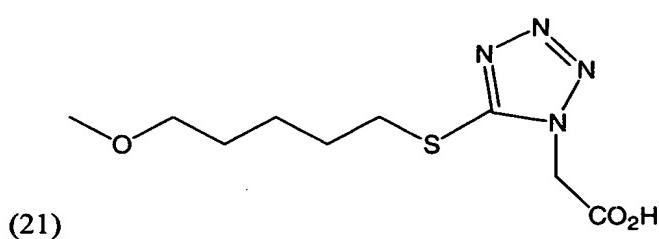
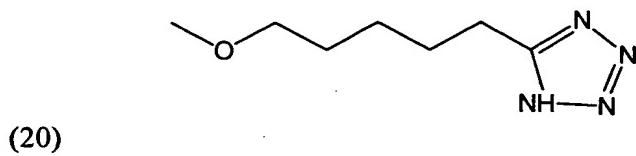
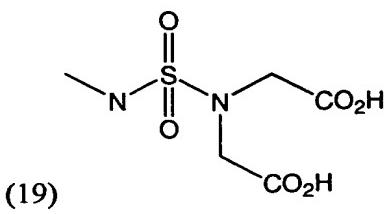
[501] 37. The compound of embodiment 35 wherein said R⁵ is attached to either a meta-position or a para-position on said phenyl ring attached to said 5-position carbon ring of said benzothiepene of said Formulas I-23 and I-24.

[502] 38. The compound of embodiments 31-37 wherein said R⁵ is selected from the group consisting of (1) - (69) and (70):

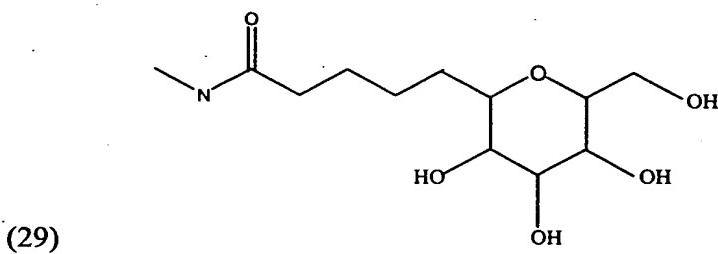
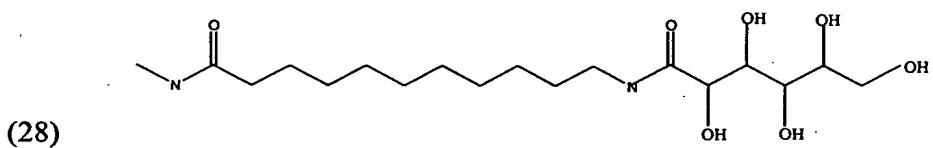
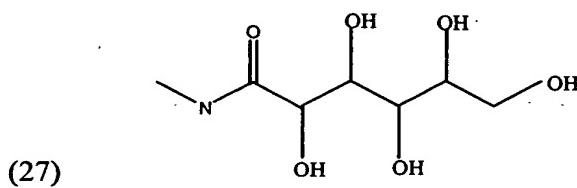
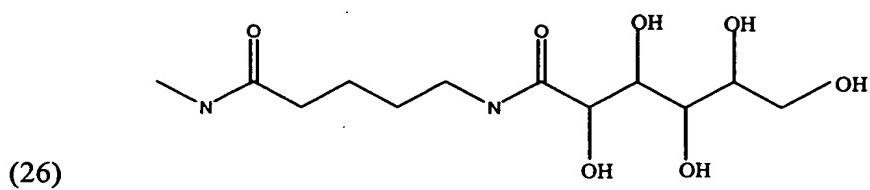
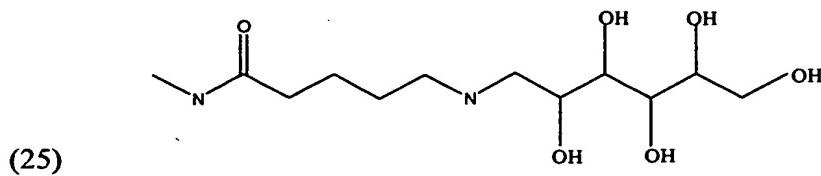


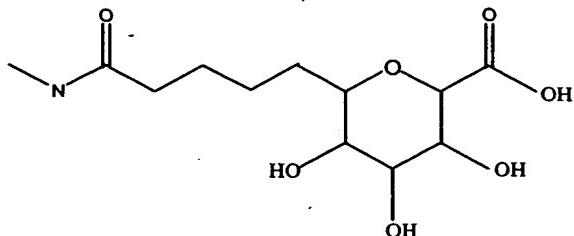




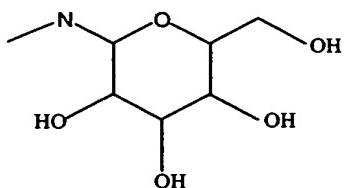


(24) $M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}

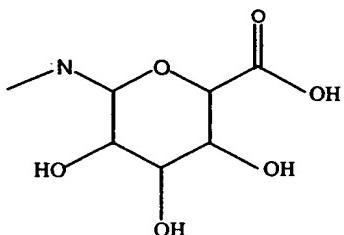




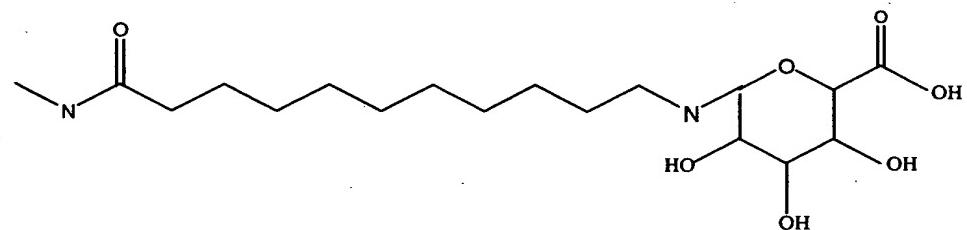
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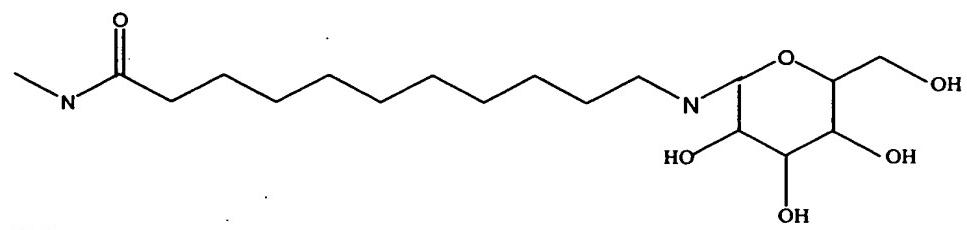
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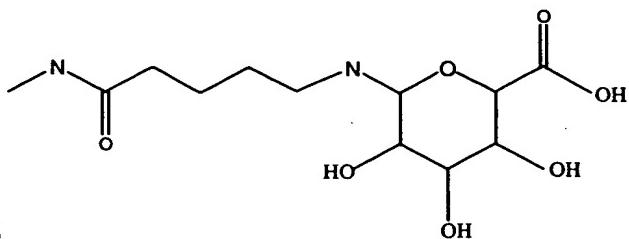
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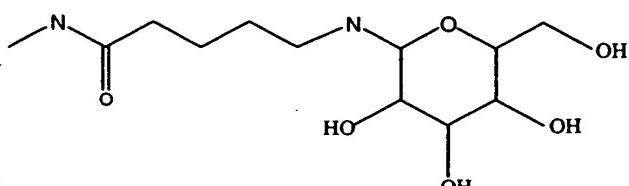
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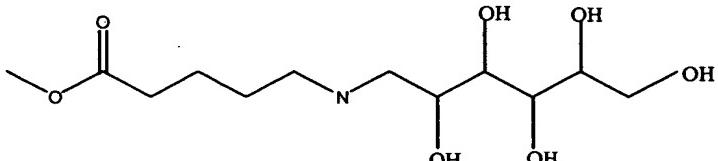
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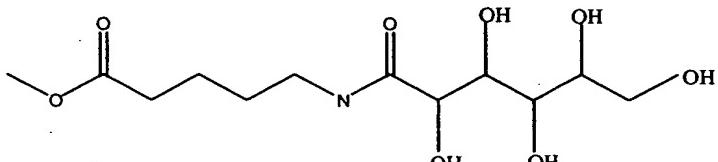
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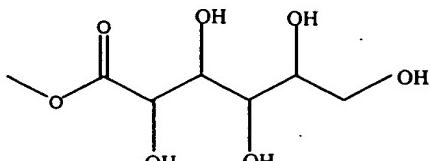
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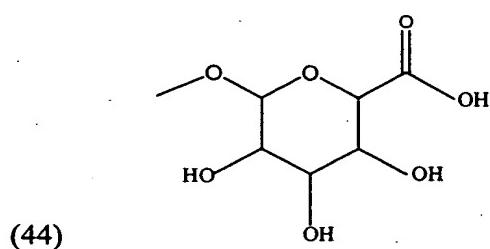
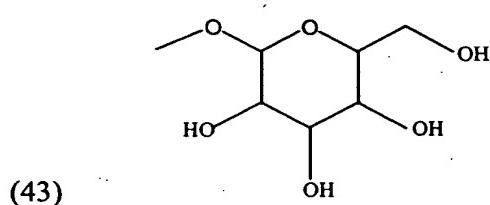
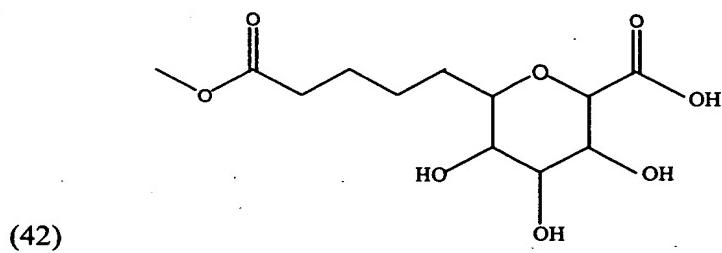
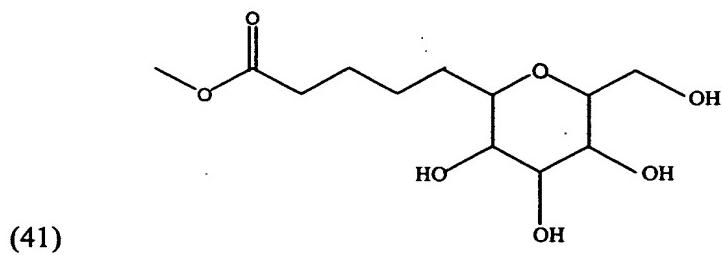
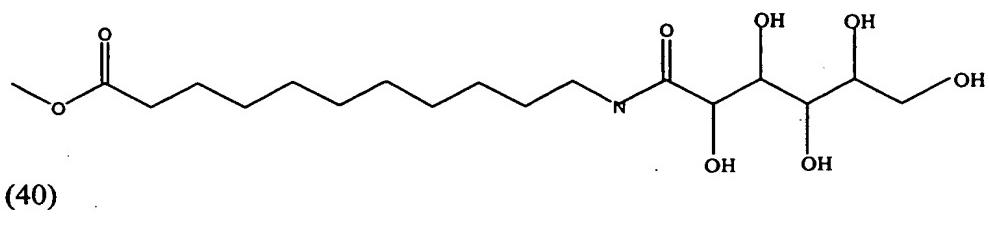
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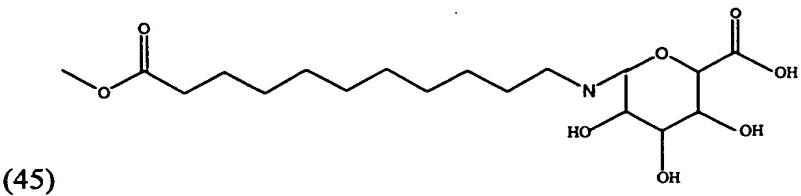


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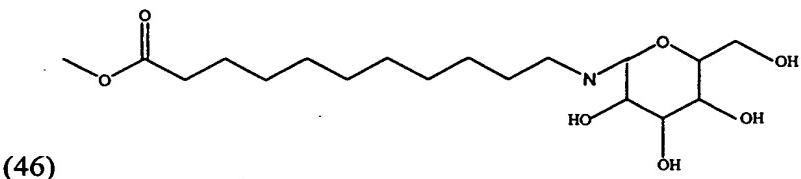


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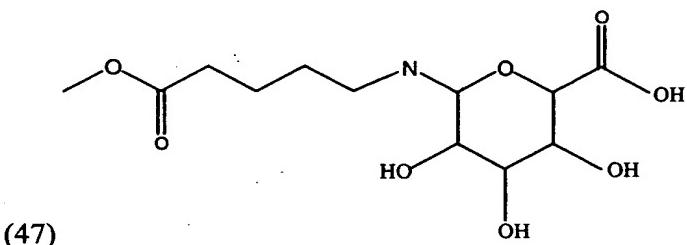




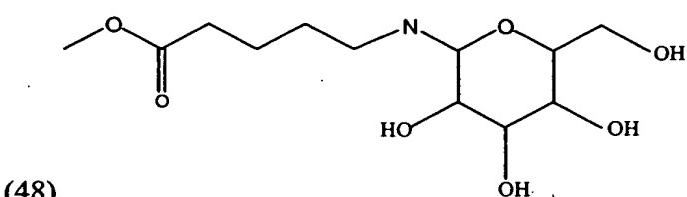
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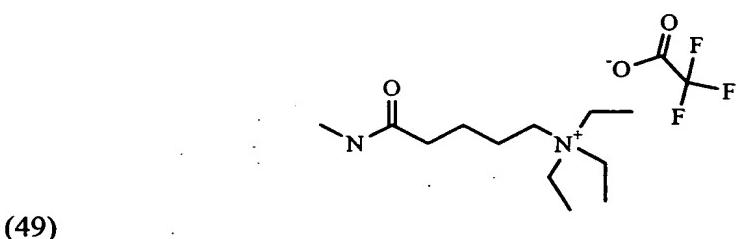
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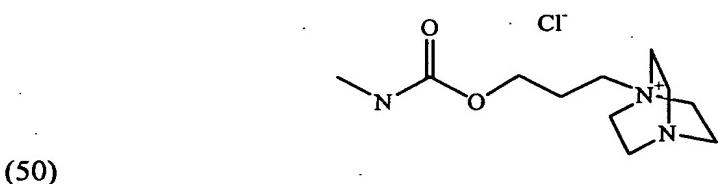
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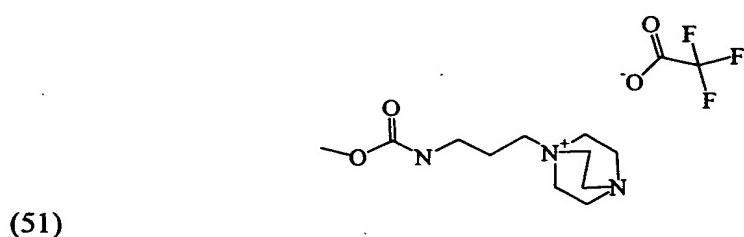
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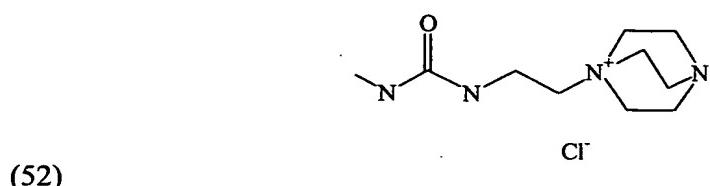
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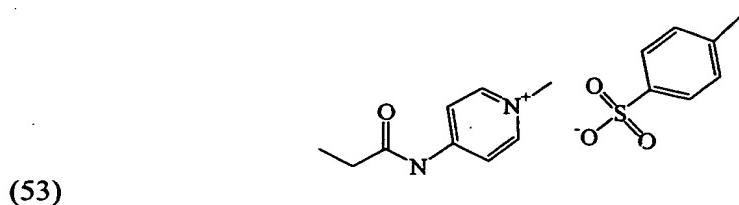
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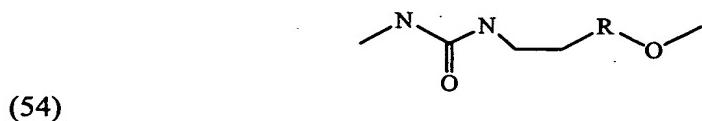
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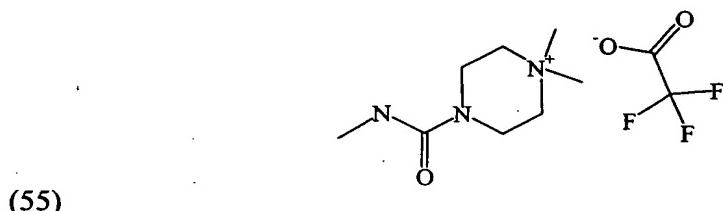
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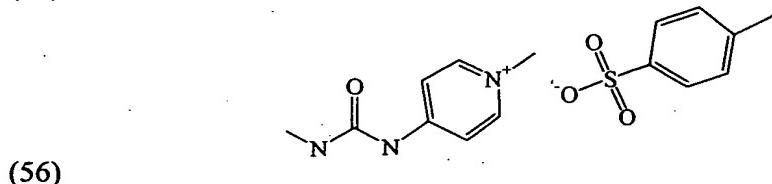
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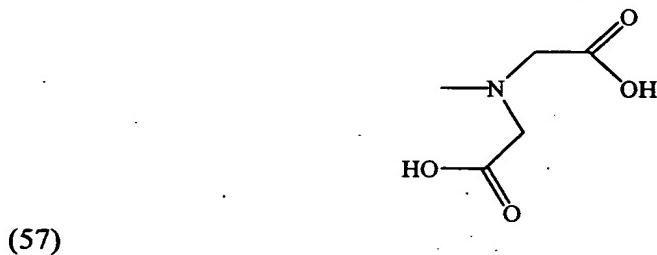
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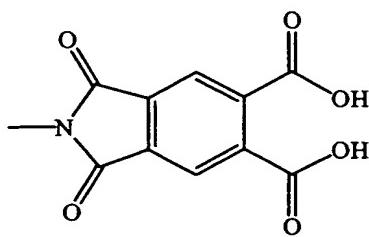
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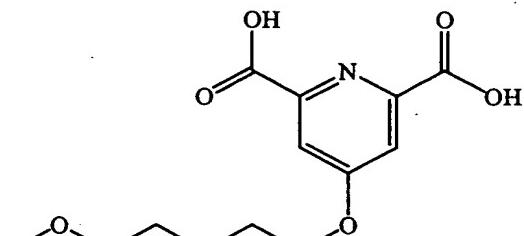
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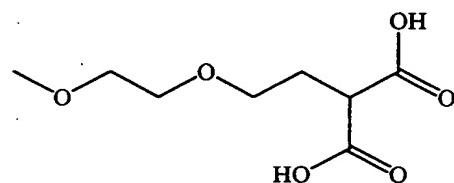
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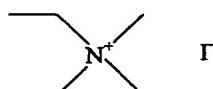
(58)



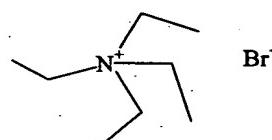
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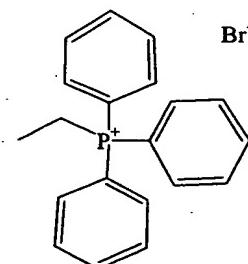
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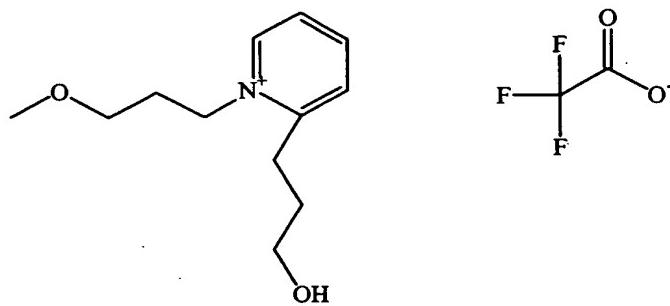
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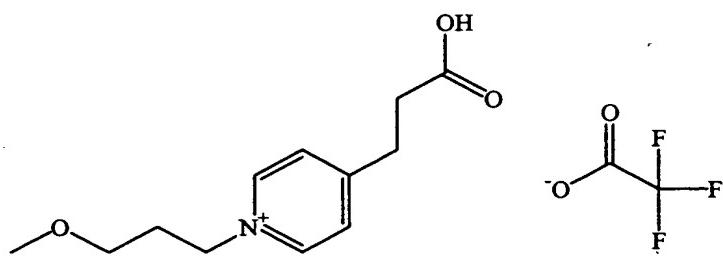
(62)



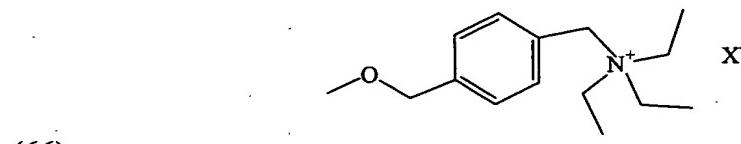
(63)



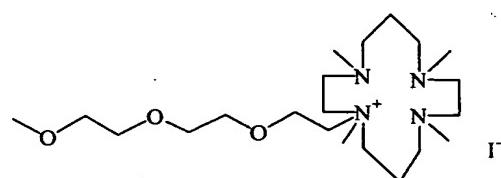
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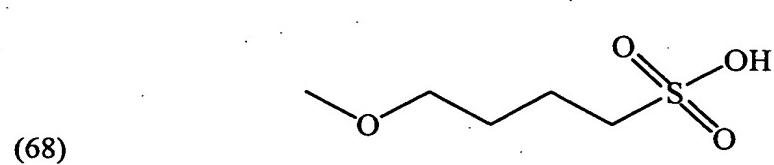
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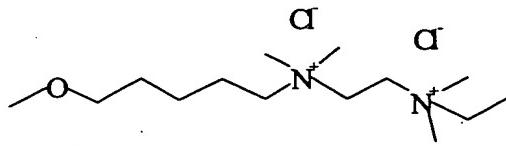
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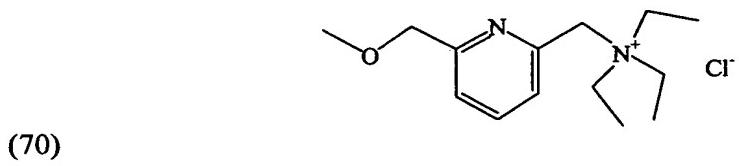
(67)



(68)



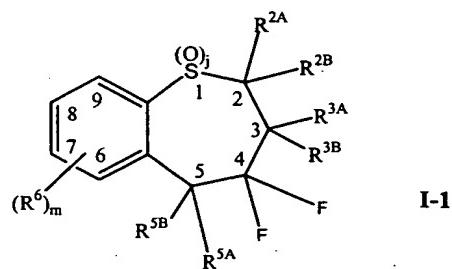
(69) and



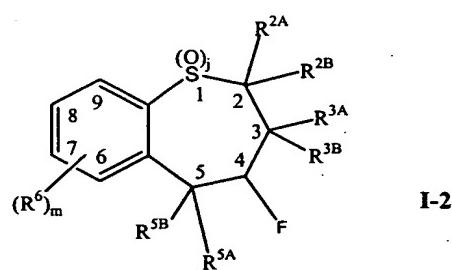
(70)

wherein when said R⁵ is said (7), said (17) or said (24), then said R^{5A} represents a left-end of said R⁵ and said R^{5B} represents a right end of said R⁵ or vice versa.

[503] 39. A method for treating a hyporelipidemic condition in a subject comprising administering to said subject in need thereof a therapeutically effective amount of a compound of Formulas I-1 or I-2, wherein said Formulas I-1 and I-2 are represented by:



I-1



I-2

or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A}, R^{3B}, R^{5A}, and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl-R⁵; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R⁵ is selected from the group consisting of hydrogen; hydrocarbyl, heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein when R⁵ is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with -NH-X-R or -O-X-R;

wherein X is selected from the group consisting of -(C=O)_s-alkyl-; -(C=O)_s-alkyl-NH-;-(C=O)_s-alkyl-O-; -(C=O)_s-alkyl-(C=O)_t; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R⁹ and R¹⁰ are as previously defined;

wherein, when R⁵ ≠ H, R⁵ is optionally substituted with one or more radicals independently selected from the group consisting of halogen; -NO₂; -CN; oxo; hydrocarbyl; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻;

wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A^- is a pharmaceutically acceptable anion;

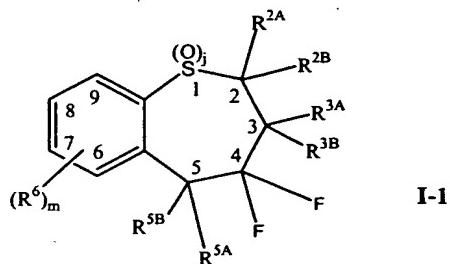
wherein M is a pharmaceutically acceptable cation;

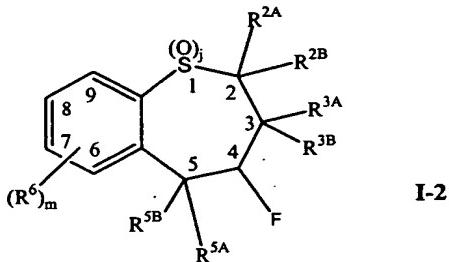
wherein one or more R^6 radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

wherein R^{13} , R^{14} , R^{15} , A^- , and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.

- [504] 40. A method of treating gallstones or a condition associated therewith in a subject comprising administering to said subject in need thereof a therapeutically effective amount of a compound of Formulas I-1 or I-2 represented by:





or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A}, R^{3B}, R^{5A}, and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl-R⁵; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R⁵ is selected from the group consisting of hydrogen; hydrocarbyl, heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein when R⁵ is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with -NH-X-R or -O-X-R;

wherein X is selected from the group consisting of -(C=O)_s-alkyl-; -(C=O)_s-alkyl-NH-; -(C=O)_s-alkyl-O-; -(C=O)_s-alkyl-(C=O)_t; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R⁹ and R¹⁰ are as previously defined;

wherein, when $R^5 \neq H$, R^5 is optionally substituted with one or more radicals independently selected from the group consisting of halogen; $-NO_2$; $-CN$; oxo; hydrocarbyl; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$;

wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A^- is a pharmaceutically acceptable anion;

wherein M is a pharmaceutically acceptable cation;

wherein one or more R^6 radicals are independently selected from the group consisting of hydrogen; halogen; $-CN$; $-NO_2$; hydrocarbyl; $-R^5$; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-S(O)_2R^{13}$; $-SO_3R^{13}$; $-S^+R^{13}R^{14}A^-$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-NR^{14}C(O)R^{13}$; $-C(O)OM$; $-S(O)NR^{13}R^{14}$; $-N^+R^{13}R^{14}R^{15}A^-$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

wherein R^{13} , R^{14} , R^{15} , A^- , and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.

[505] 41. The method of embodiment 39, wherein said subject is a mammal.

[506] 42. The method of embodiment 41, wherein said subject is a human.

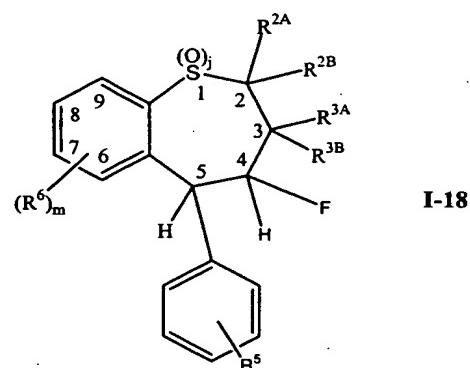
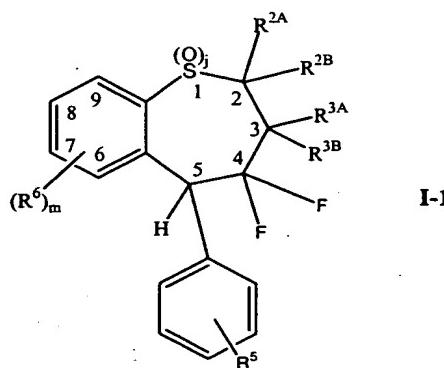
[507] 43. The method of embodiment 40 wherein said subject is a mammal.

[508] 44. The method of embodiment 43, wherein said mammal is a human.

[509] 45. The method of embodiment 39, wherein said therapeutically effective amount is administered in a single dose or in multiple divided doses.

[510] 46. The method of embodiment 40, wherein said therapeutically effective amount is administered in a single dose or in multiple divided doses.

[511] 47. A method for treating a hyperlipidemic condition in a subject comprising administering to said subject in need thereof a therapeutically effective amount of a compound of Formulas I-17 or I-18 represented by:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A} , R^{3B} , R^{5A} , and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl- R^5 ; - OR^9 ; - NR^9R^{10} ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R^5 is selected from the group consisting of hydrogen; hydrocarbyl, heterocyclyl; quaternary heterocyclyl; - OR^9 ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein when R^5 is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with - $NH-X-R$ or - $O-X-R$;

wherein X is selected from the group consisting of -($C=O)_s$ -alkyl-; -($C=O)_s$ -alkyl-NH-; -($C=O)_s$ -alkyl-O-; -($C=O)_s$ -alkyl-($C=O)_t$; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R^9 and R^{10} are as previously defined;

wherein, when $R^5 \neq H$, R^5 is optionally substituted with one or more radicals independently selected from the group consisting of halogen; - NO_2 ; - CN ; oxo; hydrocarbyl; - OR^{13} ; - $NR^{13}R^{14}$; - SR^{13} ; - $S(O)R^{13}$; - SO_2R^{13} ; - SO_3R^{13} ; - $NR^{13}OR^{14}$; - $NR^{13}NR^{14}R^{15}$; - CO_2R^{13} ; - OM ; - SO_2OM ; - $SO_2NR^{13}R^{14}$; - $C(O)NR^{13}R^{14}$; - $C(O)OM$; - COR^{13} ; - $NR^{13}C(O)R^{14}$; - $NR^{13}C(O)NR^{14}R^{15}$; - $NR^{13}CO_2R^{14}$; - $OC(O)R^{13}$; - $OC(O)NR^{13}R^{14}$; - $NR^{13}SOR^{14}$; - $NR^{13}SO_2R^{14}$; - $NR^{13}SONR^{14}R^{15}$; - $NR^{13}SO_2NR^{14}R^{15}$; - $PR^{13}R^{14}$; - $P(O)R^{13}R^{14}$; - $P^+R^{13}R^{14}R^{15}A^-$; - $P(OR^{13})OR^{14}$; - $S^+R^{13}R^{14}A^-$; and - $N^+R^{13}R^{14}R^{15}A^-$;

wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A^- is a pharmaceutically acceptable anion;

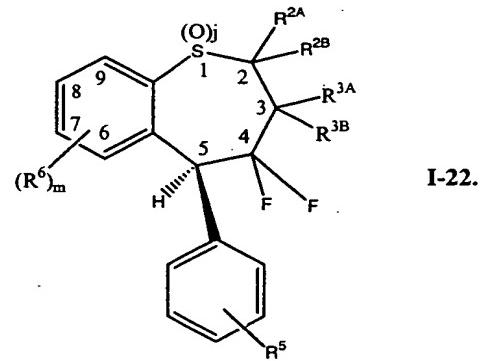
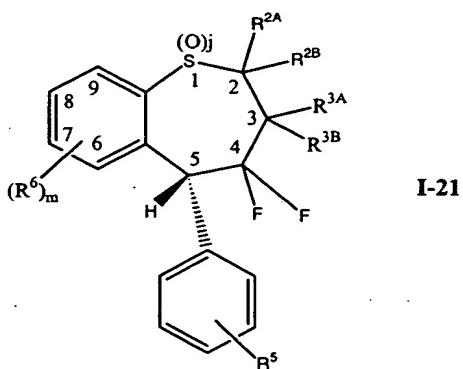
wherein M is a pharmaceutically acceptable cation;

wherein one or more R⁶ radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

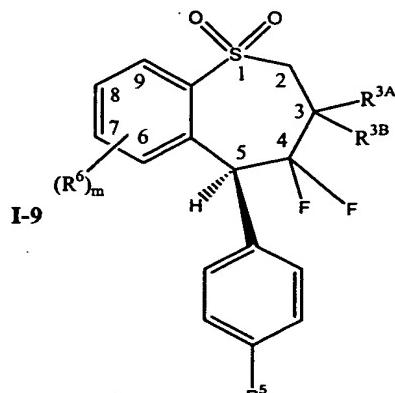
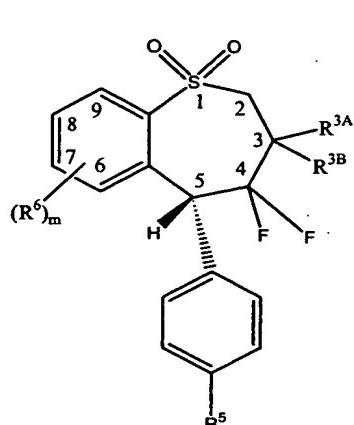
wherein R¹³, R¹⁴, R¹⁵, A⁻, and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.

[512] 48. The method of embodiment 47 wherein said Formula I-17 comprises a member selected from the group consisting of I-21 and I-22 represented by:

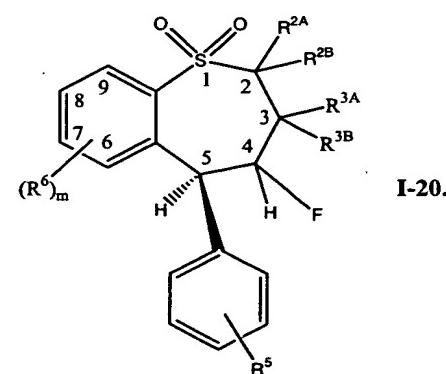
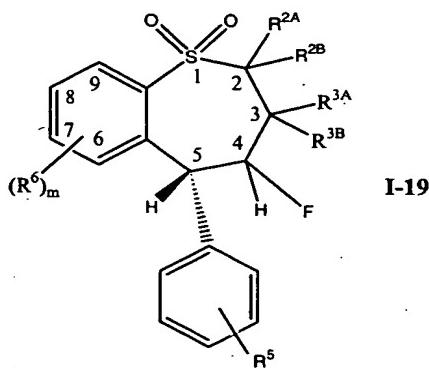


[513] 49. The method of embodiment 48 wherein said Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:

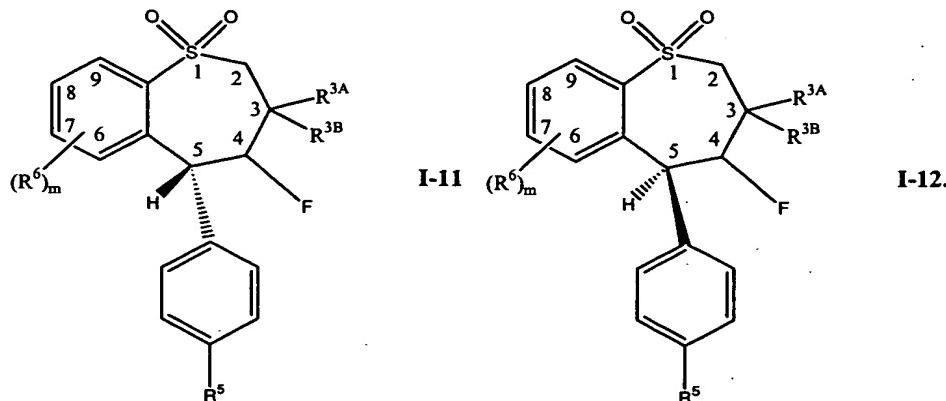


I-10.

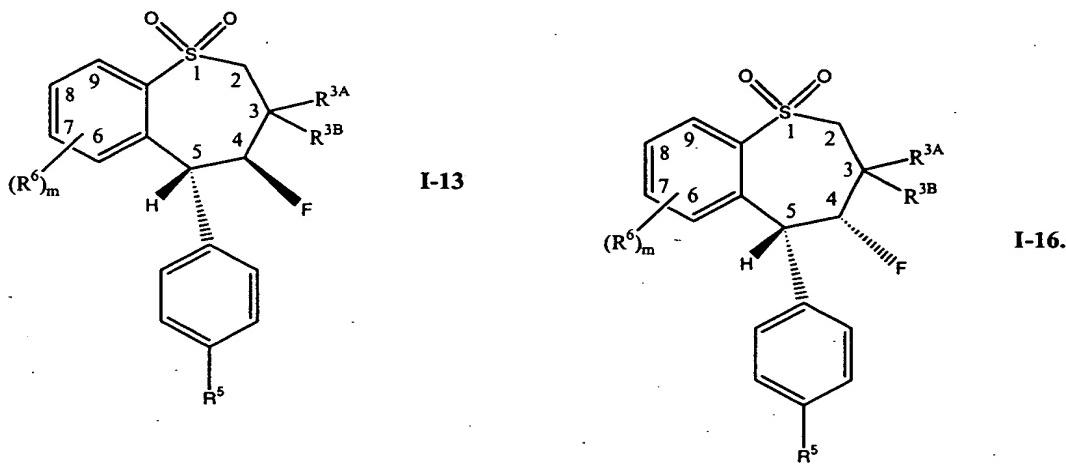
[514] 50. The method of embodiment 47 wherein said Formula I-18 comprises a member selected from the group consisting of I-19 and I-20 represented by:



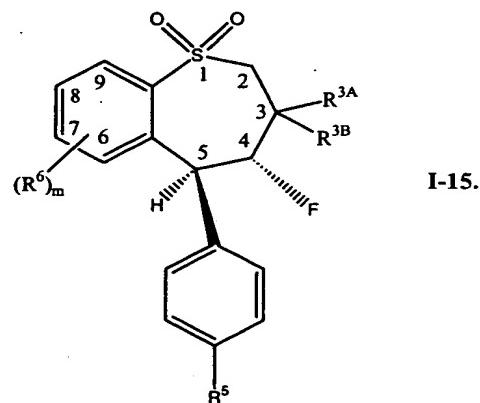
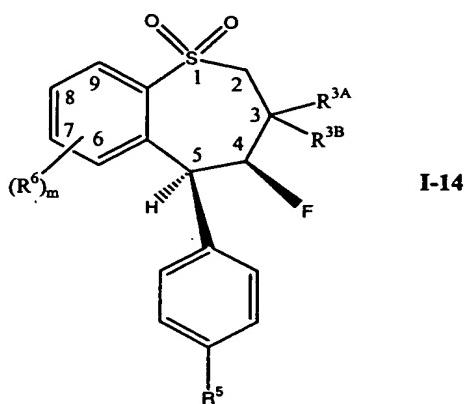
[515] 51. The method of embodiment 50 wherein said Formulas I-19 and I-20 comprise Formulas I-11 and I-12, respectively, represented by:



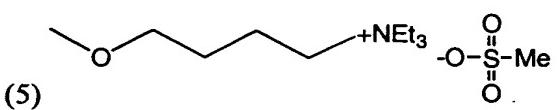
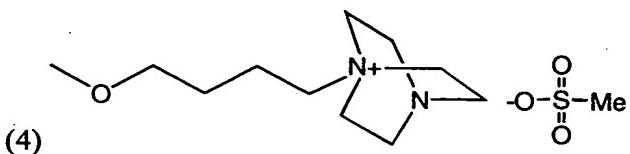
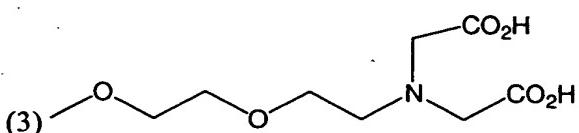
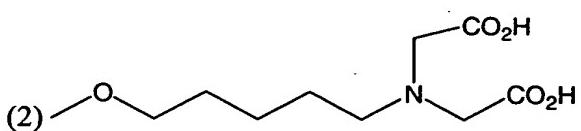
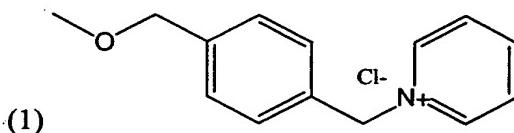
[516] 52. The method of embodiment 51 where said Formula I-11 comprises a member selected from the group consisting of Formulas I-13 and I-16 represented by:

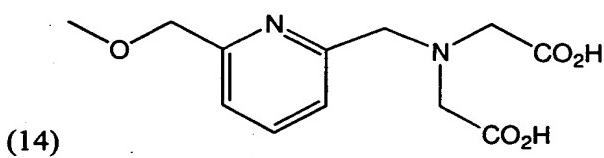
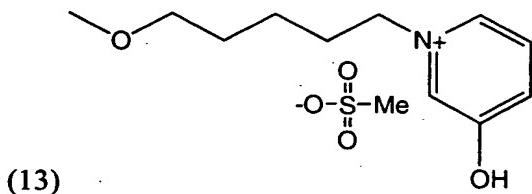
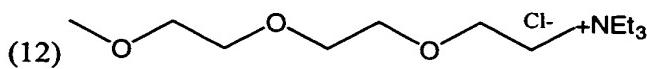
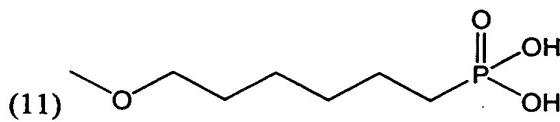
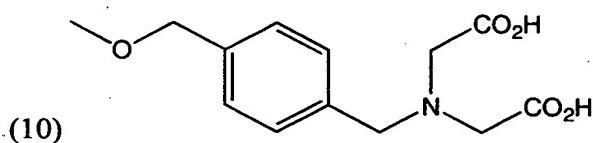
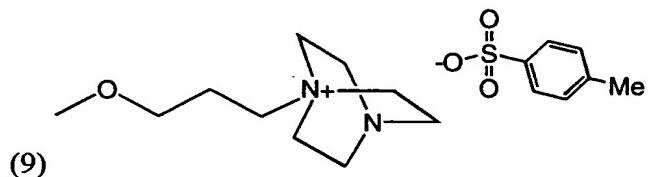
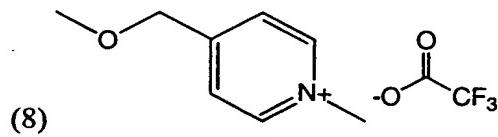
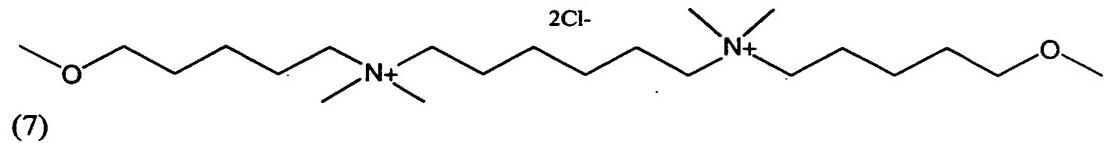
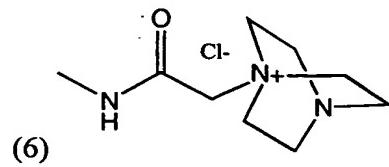


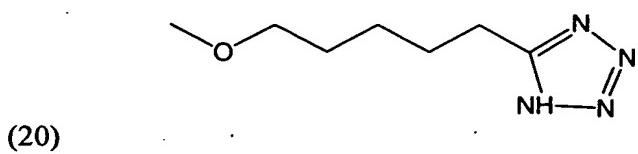
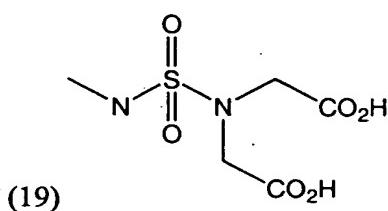
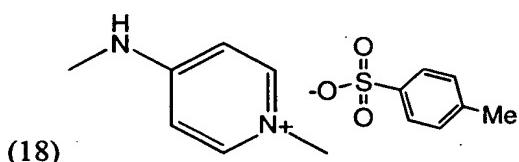
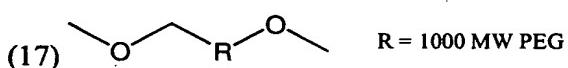
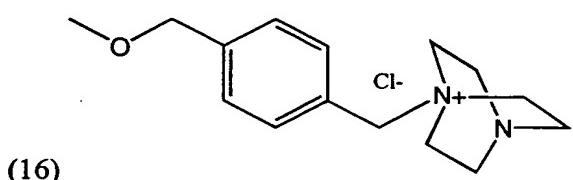
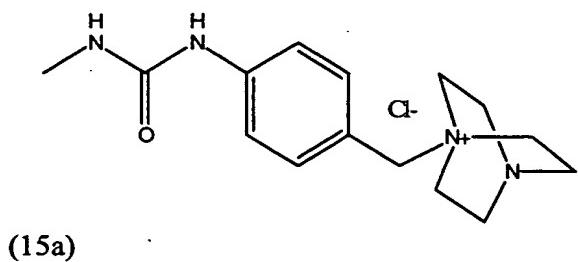
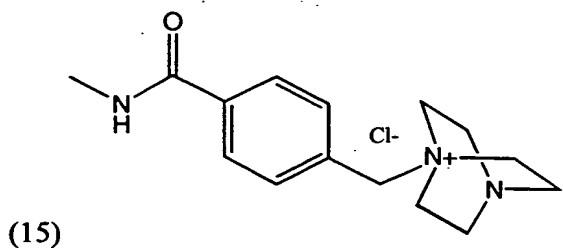
[517] 53. The method of embodiment 51 wherein said Formula I-12 comprises a member selected from the group consisting of Formulas I-14 and I-15 represented by:

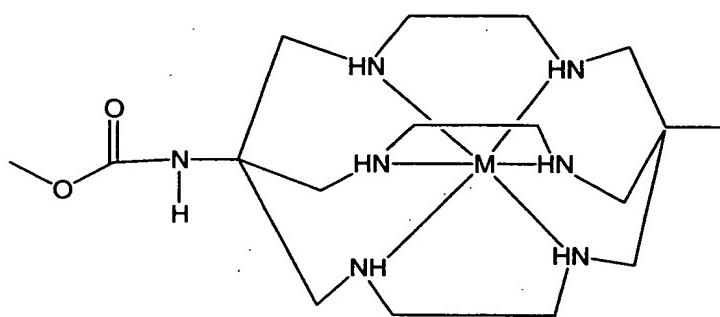
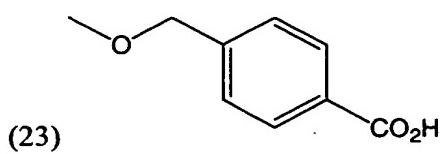
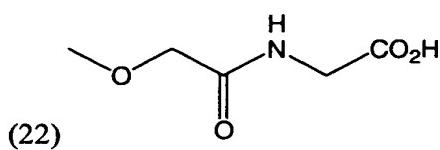
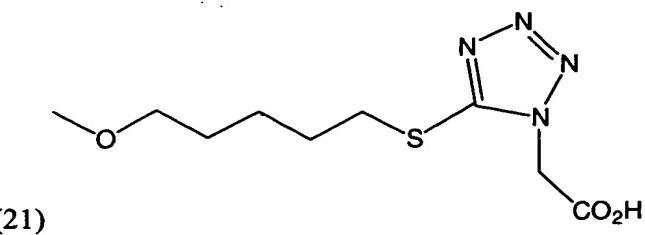


[518] 54. The method of embodiments 47-53 wherein said R⁵ is a member selected from the group consisting of (1) - (69) and (70):

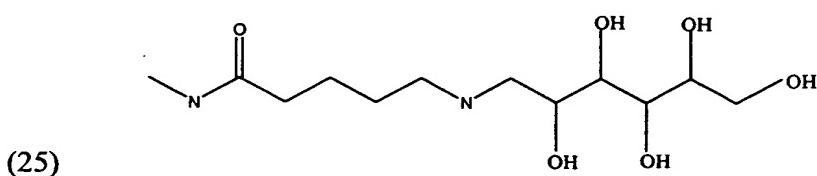


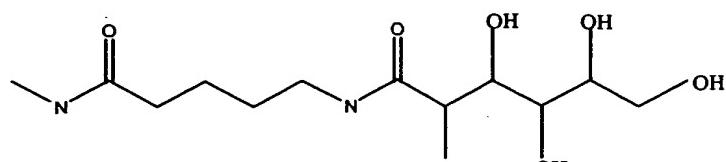




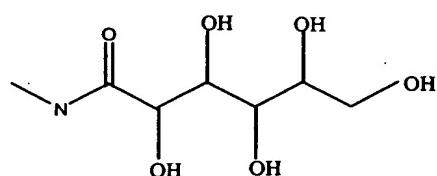


(24) $M = \text{Co}^{\text{II}}, ^{\text{III}}$, $\text{Mn}^{\text{II}}, ^{\text{III}}$, $\text{Fe}^{\text{II}}, ^{\text{III}}$, $\text{Ni}^{\text{II}}, ^{\text{III}}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}

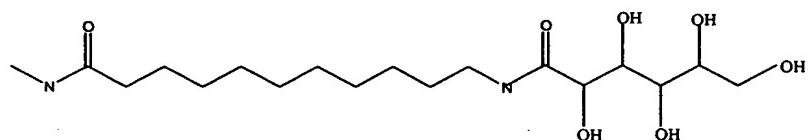




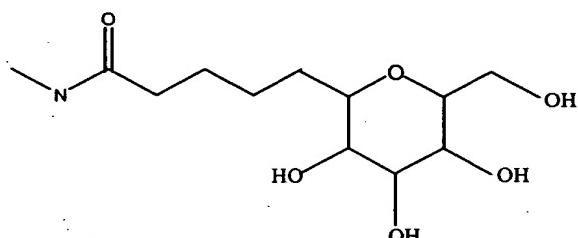
(26)



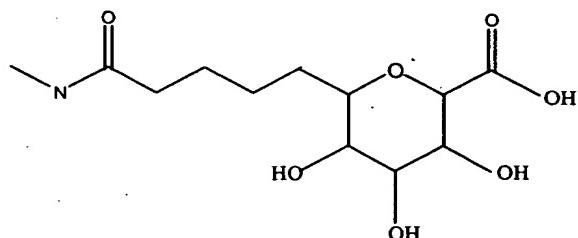
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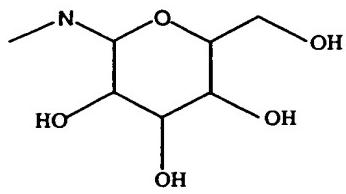
(28)



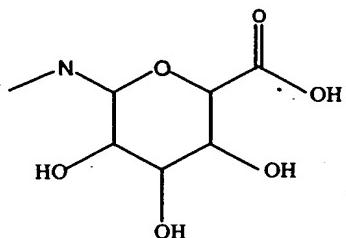
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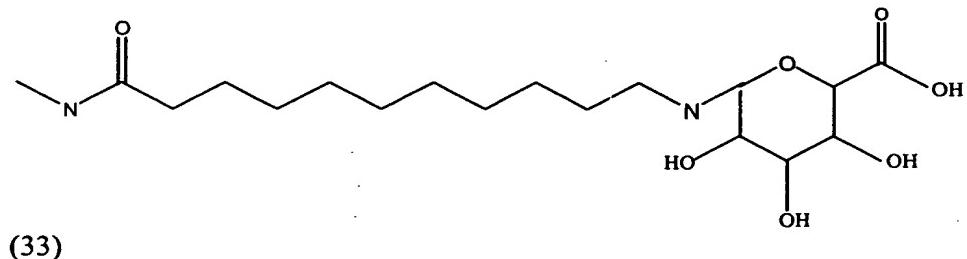
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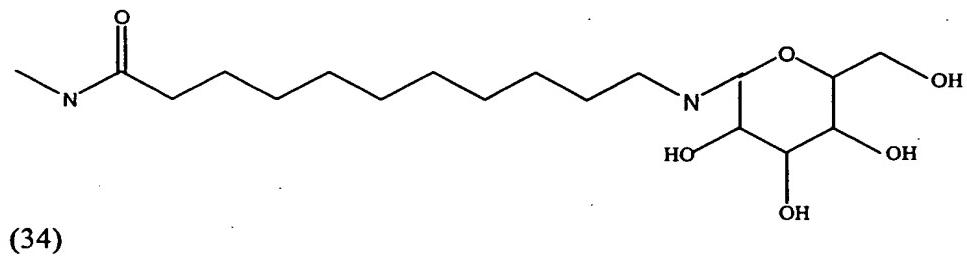
(31)



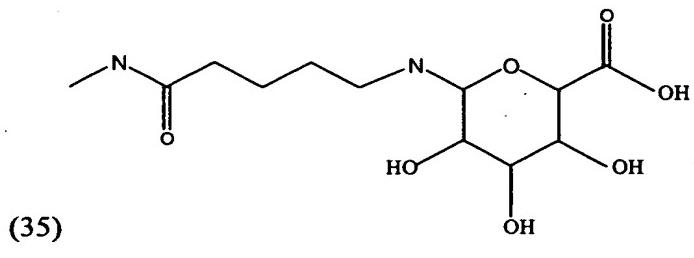
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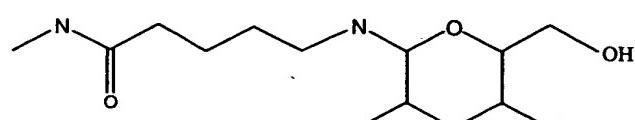
(33)



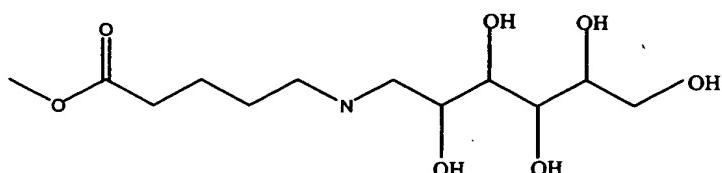
(34)



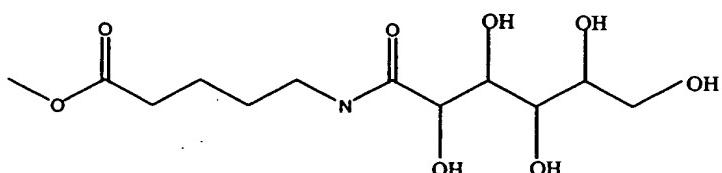
(35)



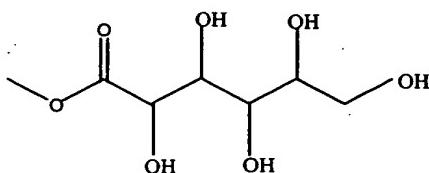
(36)



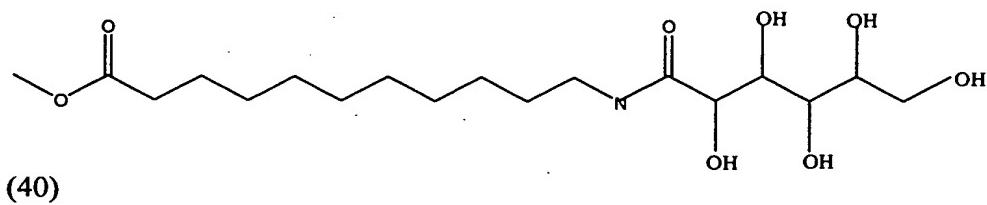
(37)



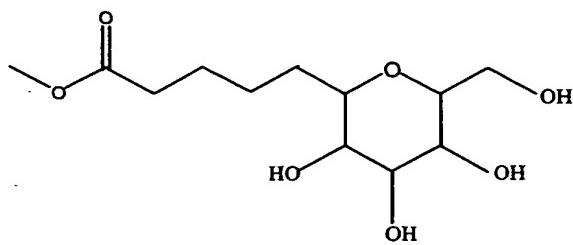
(38)



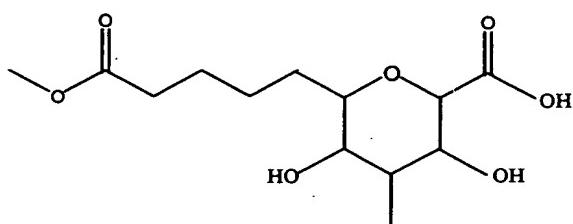
(39)



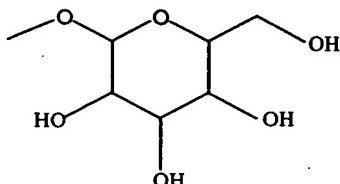
(40)



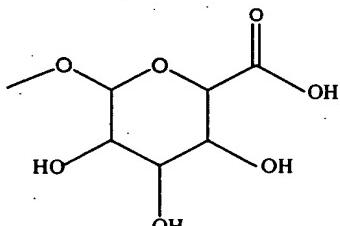
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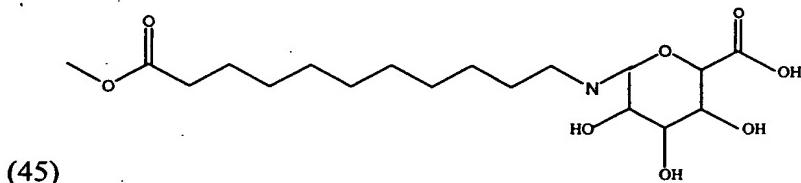
(42)



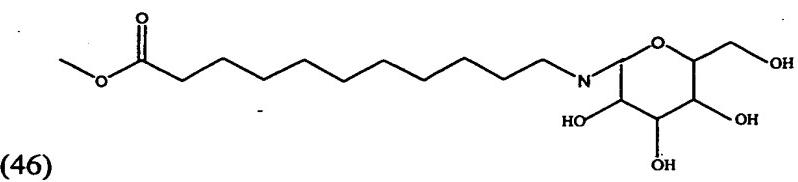
(43)



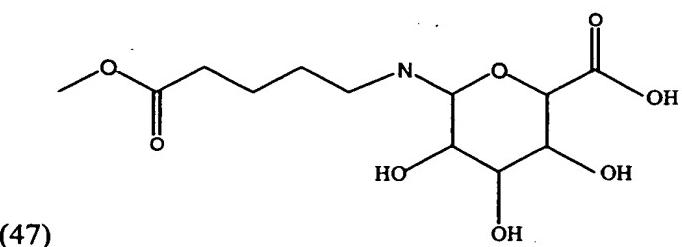
(44)



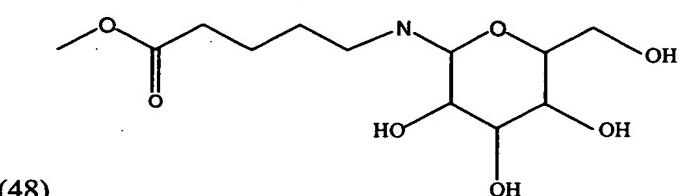
(45)



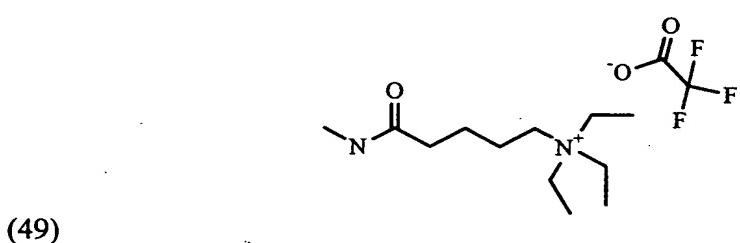
(46)



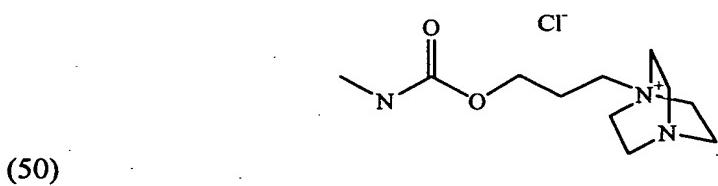
(47)



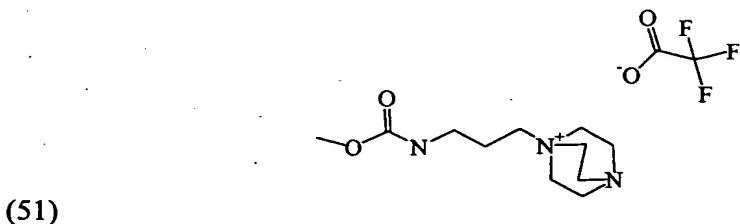
(48)



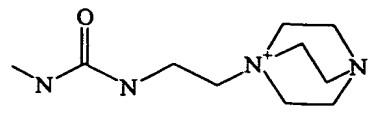
(49)



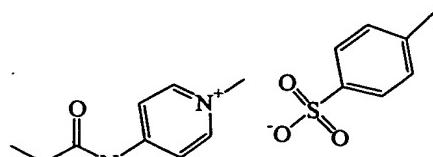
(50)



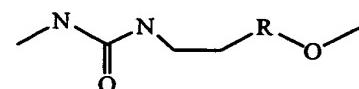
(51)



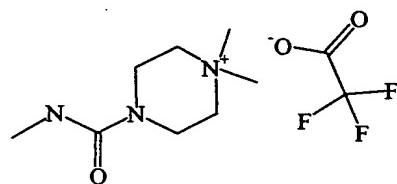
(52)



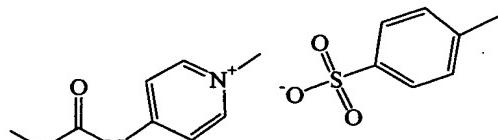
(53)



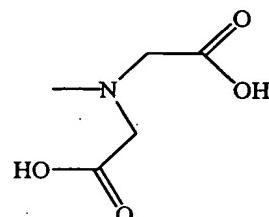
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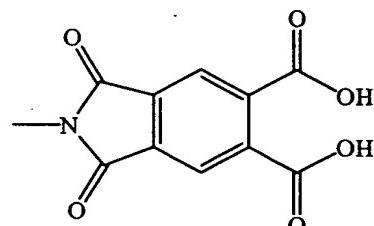
(55)



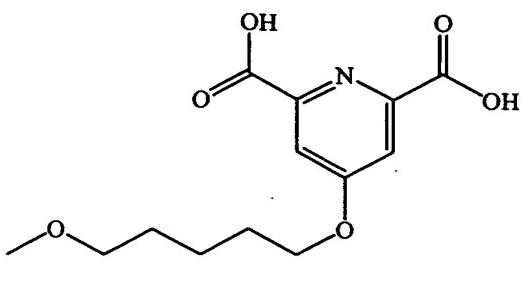
(56)



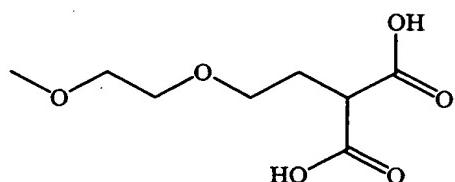
(57)



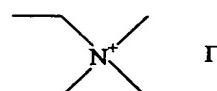
(58)



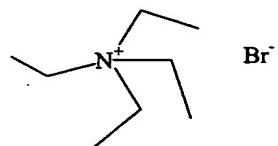
(59)



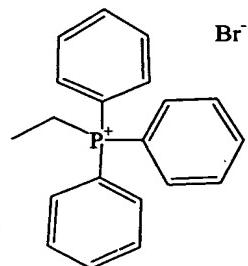
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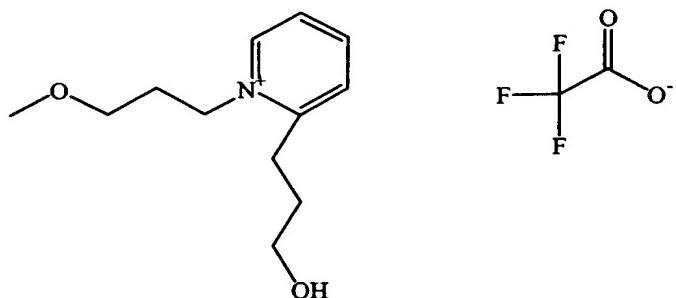
(61)



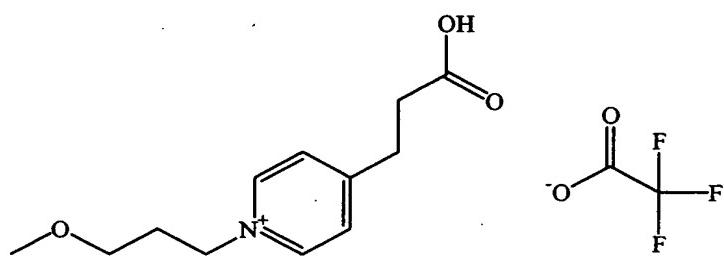
(62)



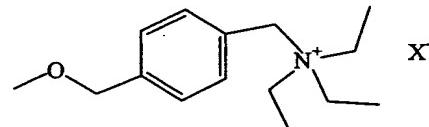
(63)



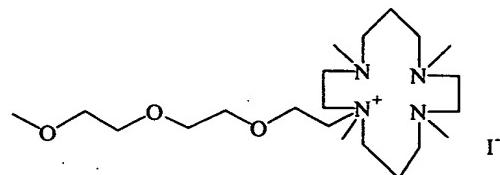
(64)



(65)

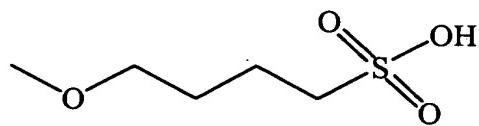


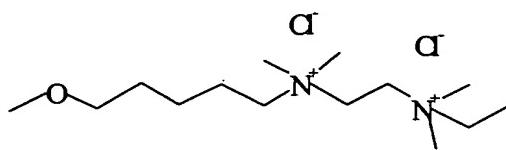
(66)



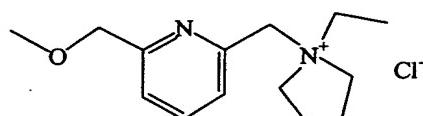
(67)

(68)





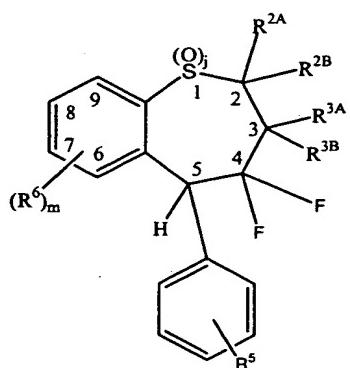
(69) and



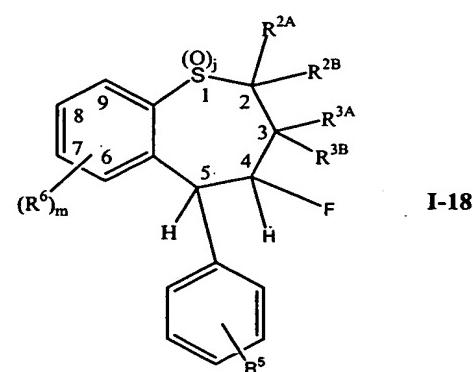
(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

[519] 55. A method for treating gallstones or a condition associated therewith in a subject in need thereof, said method comprising administering a therapeutically effective amount of a compound of Formulas I-17 or I-18 represented by:



I-17



I-18

or a pharmaceutically acceptable salt, solvate, or prodrug thereof
wherein j is 0, 1 or 2;
wherein m is 0, 1, 2, 3 or 4;
wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A} , R^{3B} , R^{5A} , and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl- R^5 ; - OR^9 ; - NR^9R^{10} ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R^5 is selected from the group consisting of hydrogen; hydrocarbyl, heterocyclyl; quaternary heterocyclyl; - OR^9 ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein when R^5 is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with - $NH-X-R$ or - $O-X-R$;

wherein X is selected from the group consisting of -($C=O)_s$ -alkyl-; -($C=O)_s$ -alkyl-NH-; -($C=O)_s$ -alkyl-O-; -($C=O)_s$ -alkyl-($C=O)_t$; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R^9 and R^{10} are as previously defined;

wherein, when $R^5 \neq H$, R^5 is optionally substituted with one or more radicals independently selected from the group consisting of halogen; - NO_2 ; - CN ; oxo; hydrocarbyl; - OR^{13} ; - $NR^{13}R^{14}$; - SR^{13} ; - $S(O)R^{13}$; - SO_2R^{13} ; - SO_3R^{13} ; - $NR^{13}OR^{14}$; - $NR^{13}NR^{14}R^{15}$; - CO_2R^{13} ; - OM ; - SO_2OM ; - $SO_2NR^{13}R^{14}$; - $C(O)NR^{13}R^{14}$; - $C(O)OM$; - COR^{13} ; - $NR^{13}C(O)R^{14}$; - $NR^{13}C(O)NR^{14}R^{15}$; - $NR^{13}CO_2R^{14}$; - $OC(O)R^{13}$; - $OC(O)NR^{13}R^{14}$; - $NR^{13}SOR^{14}$; - $NR^{13}SO_2R^{14}$; - $NR^{13}SONR^{14}R^{15}$; - $NR^{13}SO_2NR^{14}R^{15}$; - $PR^{13}R^{14}$; - $P(O)R^{13}R^{14}$; - $P^+R^{13}R^{14}R^{15}A^-$; - $P(OR^{13})OR^{14}$; - $S^+R^{13}R^{14}A^-$; and - $N^+R^{13}R^{14}R^{15}A^-$;

wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A^- is a pharmaceutically acceptable anion;

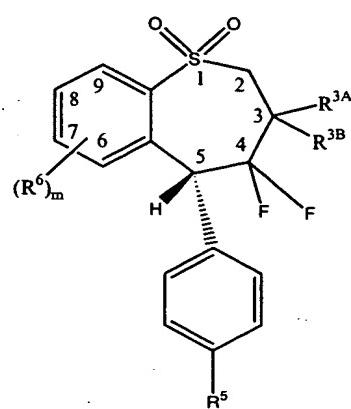
wherein M is a pharmaceutically acceptable cation;

wherein one or more R⁶ radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -S(O)NR¹³R¹⁴; -N⁺R¹³R¹⁴R¹⁵A⁻; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

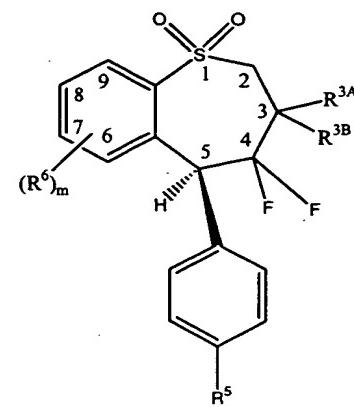
wherein R¹³, R¹⁴, R¹⁵, A⁻, and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof.

[520] 56. The method of embodiment 55 wherein said Formula I-17 comprises a member selected from the group consisting of I-21 and I-22 represented by:

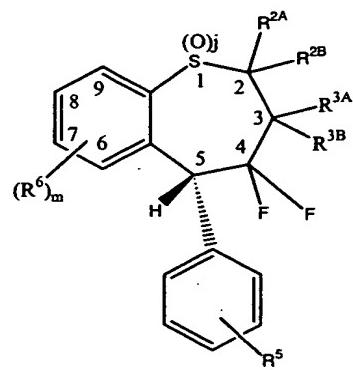


I-9

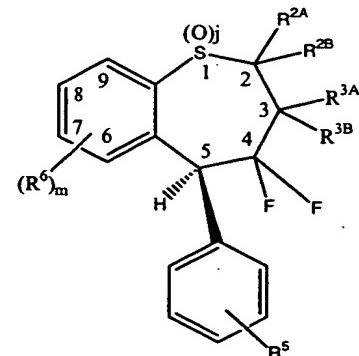


I-10.

[521] 57. The method of embodiment 56 wherein said Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:

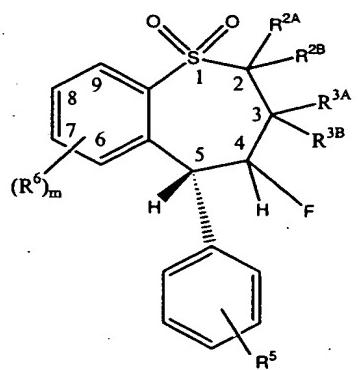


I-21

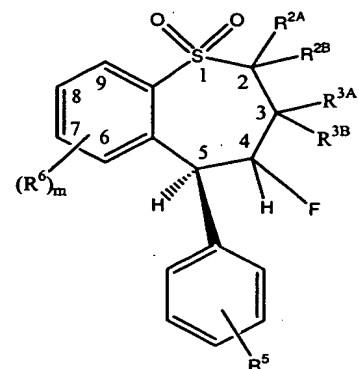


I-22.

[522] 58. The method of embodiment 57 wherein said Formula I-18 comprises a member selected from the group consisting of I-19 and I-20 represented by:

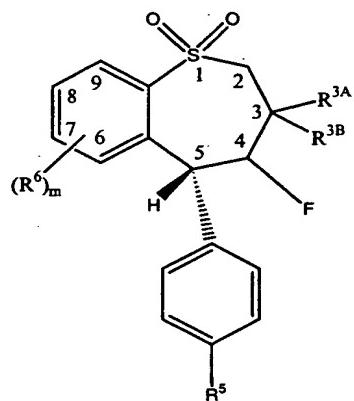


I-19

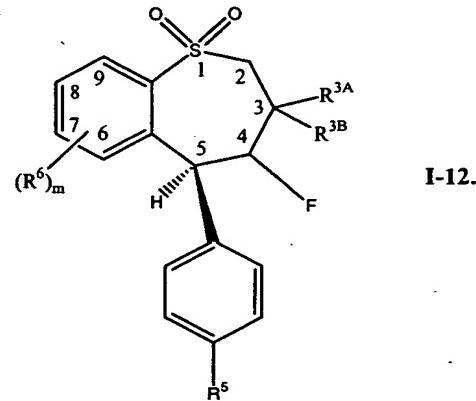


I-20.

[523] 59. The method of embodiment 58 wherein said Formulas I-19 and I-20 comprise Formulas I-11 and I-12, respectively, represented by:

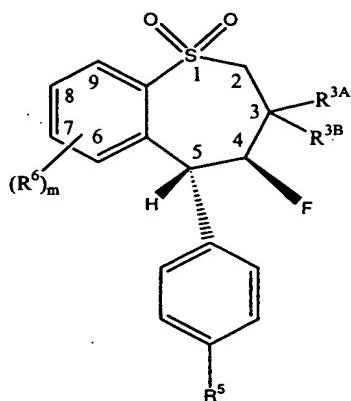


I-11

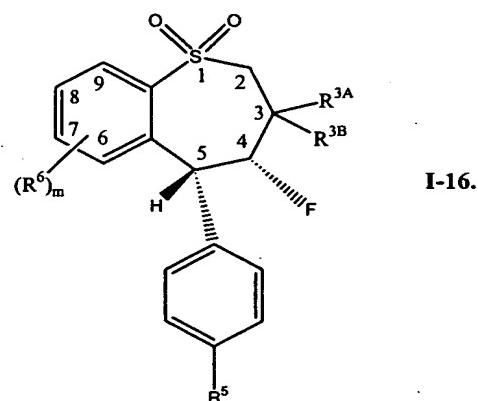


I-12.

[524] 60. The method of embodiment 59 wherein said Formula I-11 comprises a member selected from the group consisting of Formulas I-13 and I-16 represented by:

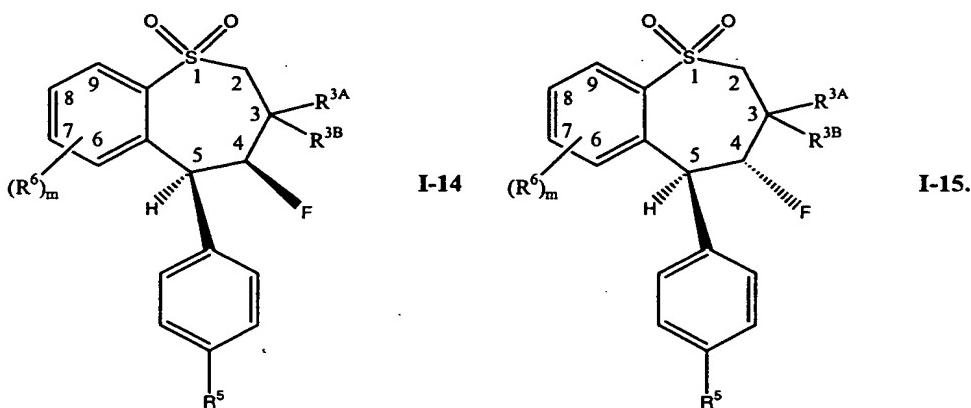


I-13

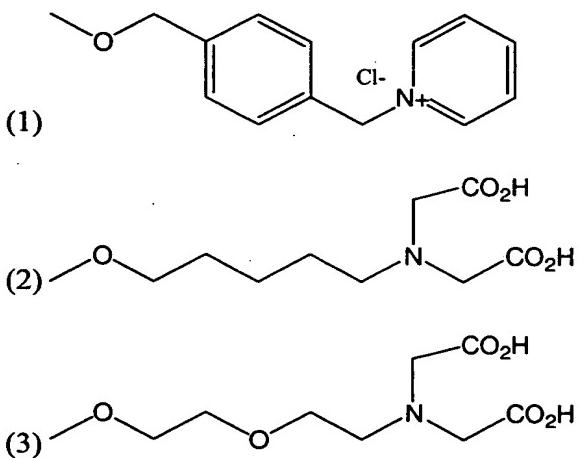


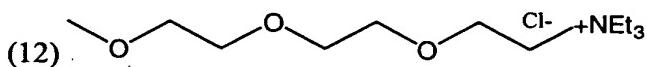
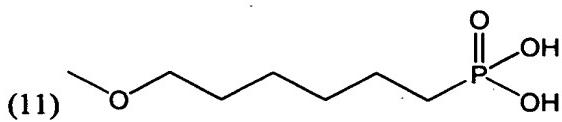
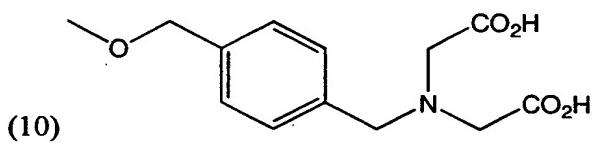
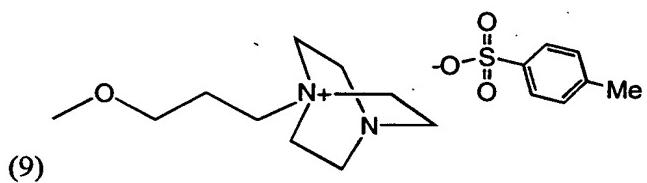
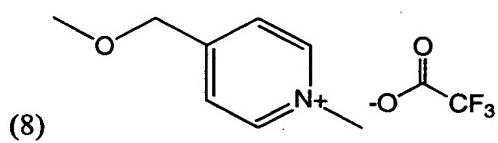
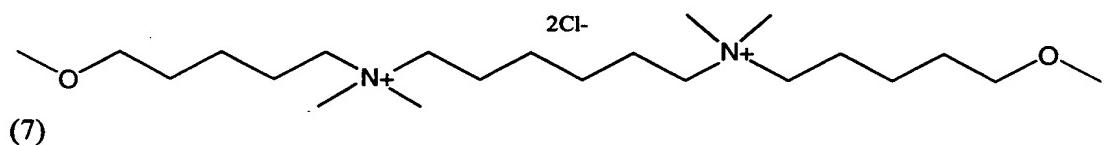
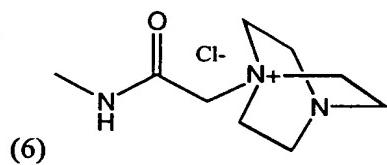
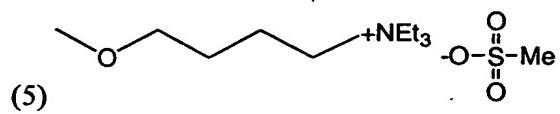
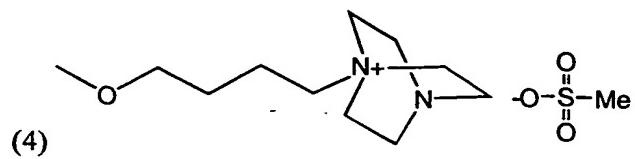
I-16.

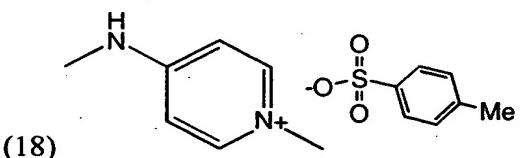
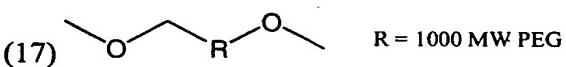
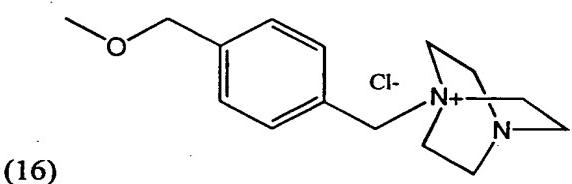
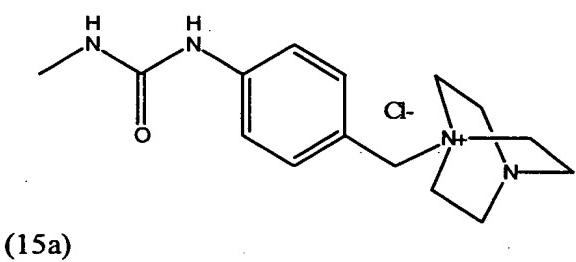
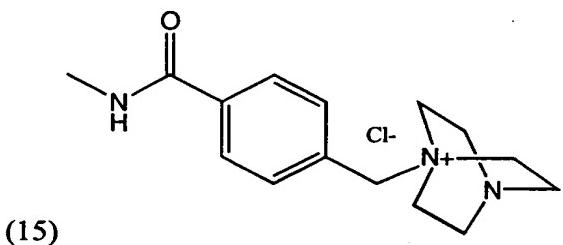
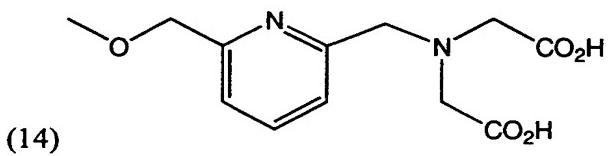
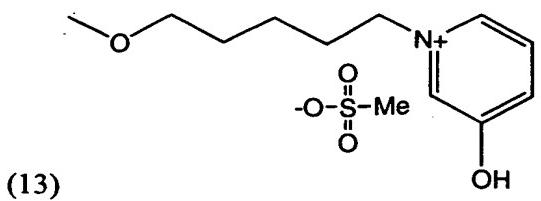
[525] 61. The method of embodiment 59 wherein said Formula I-12 comprises a member selected from the group consisting of Formulas I-14 and I-15 represented by:

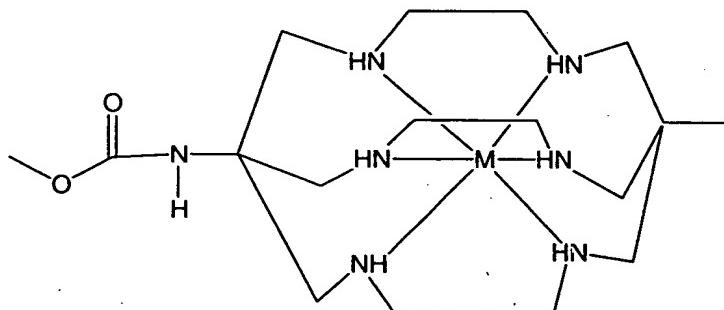
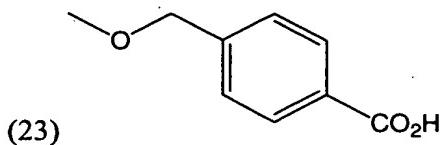
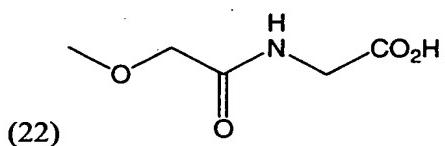
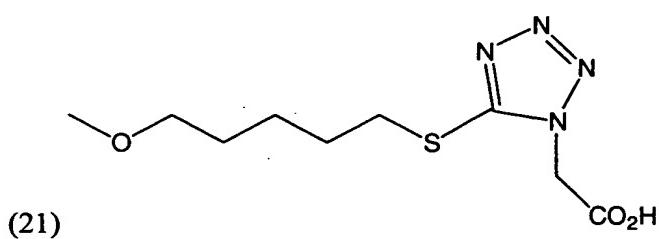
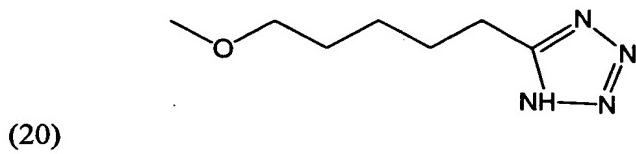
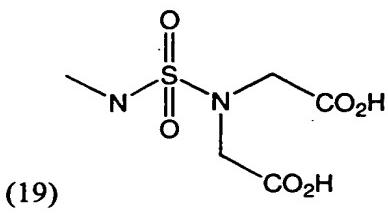


[526] 62. The method of embodiments 55 - 61 wherein said R⁵ is a member selected from the group consisting of (1) - (69) and (70):

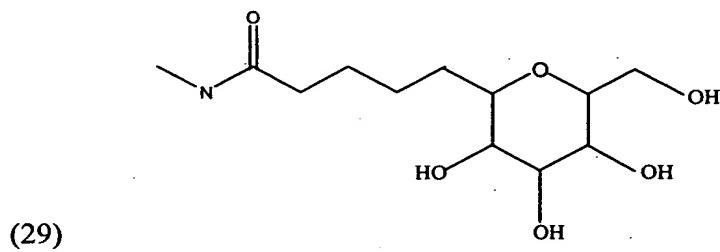
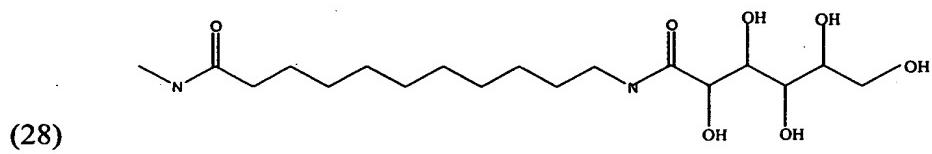
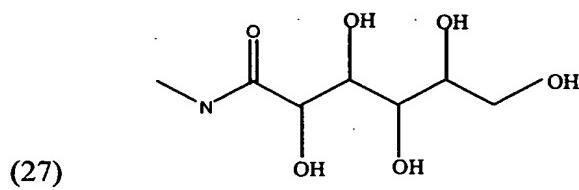
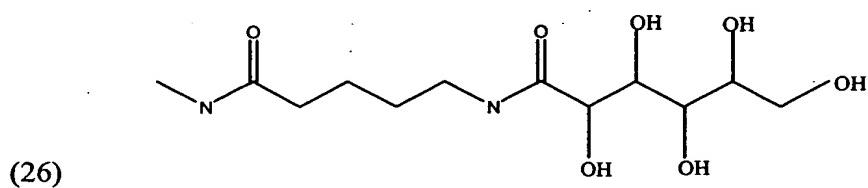
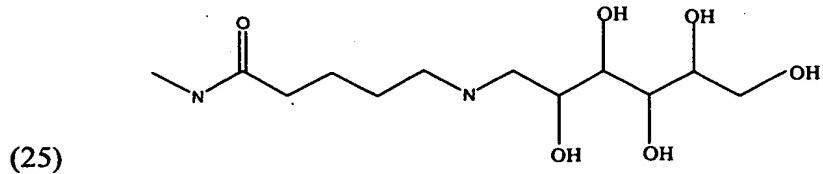


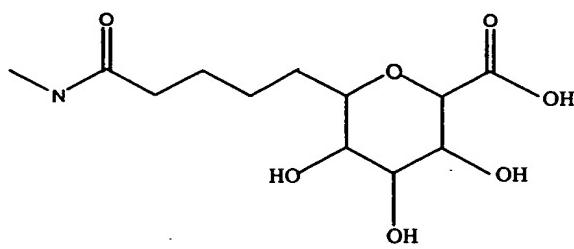




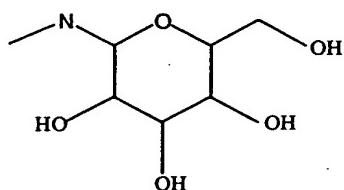


(24) $M = \text{Co}^{\text{II}}, \text{III}, \text{Mn}^{\text{II}}, \text{III}, \text{Fe}^{\text{II}}, \text{III}, \text{Ni}^{\text{II}}, \text{III},$
 $\text{Cr}^{\text{III}}, \text{Cu}^{\text{II}}, \text{Zn}^{\text{II}}, \text{Cd}^{\text{II}}, \text{Ga}^{\text{III}}, \text{In}^{\text{III}}, \text{V}^{\text{IV}},$
 $\text{Ru}^{\text{II}}, \text{Pr}^{\text{IV}}, \text{Rh}^{\text{III}} \text{ or Ir}^{\text{III}}$

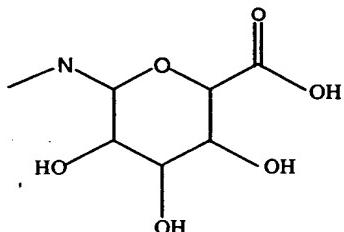




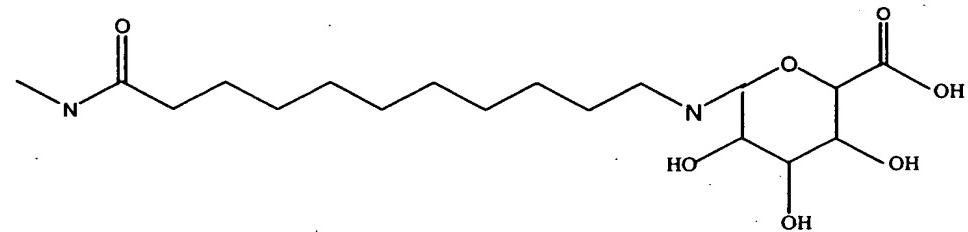
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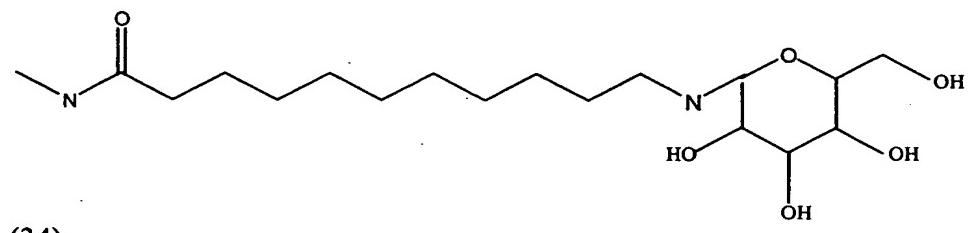
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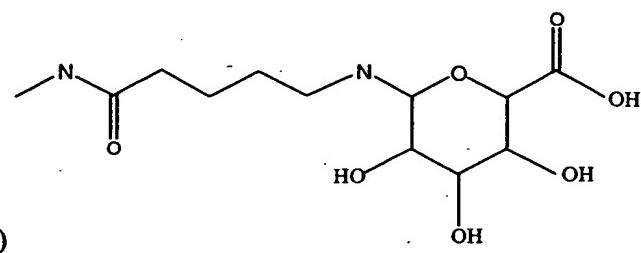
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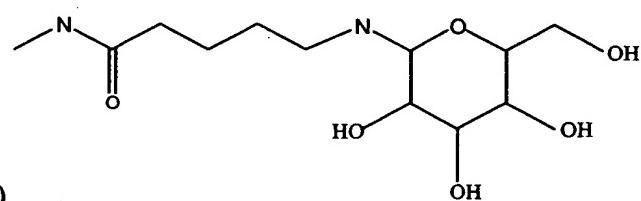
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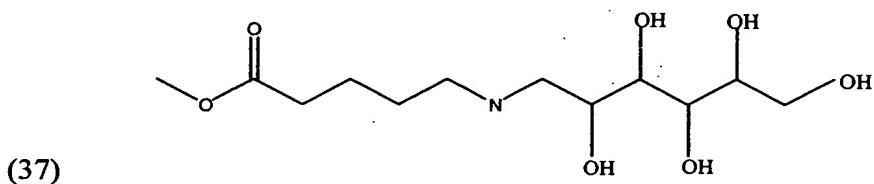
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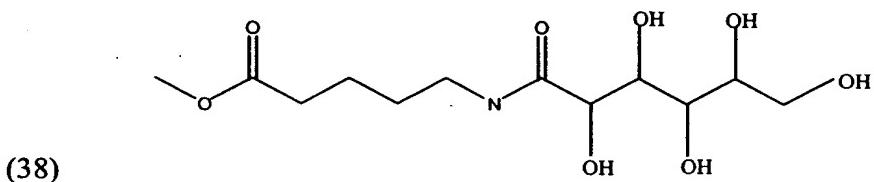
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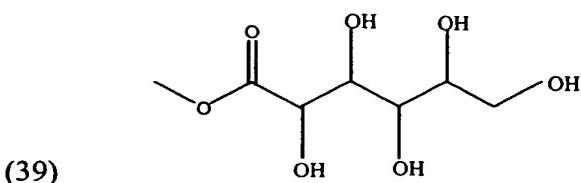
(36)



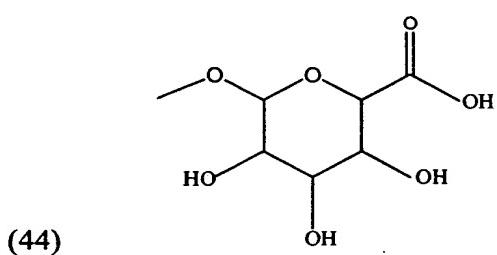
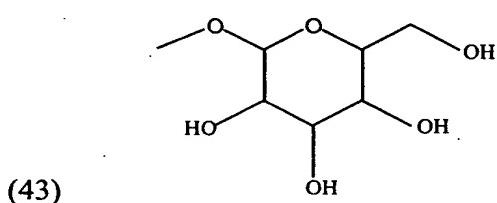
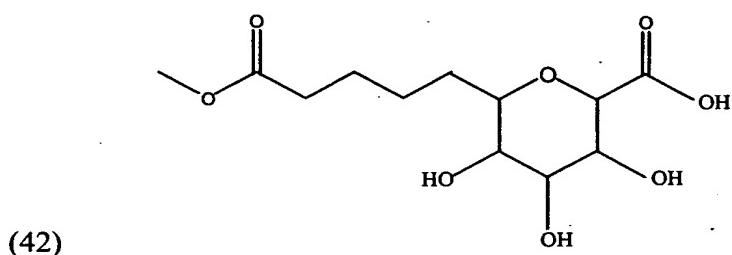
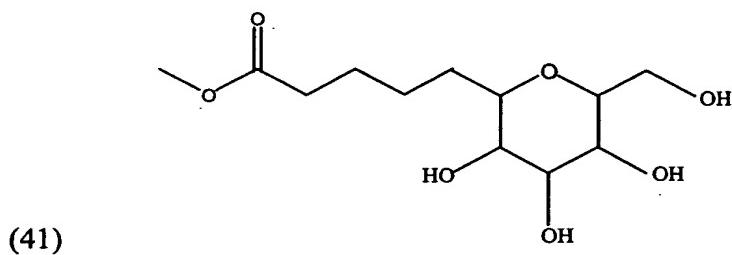
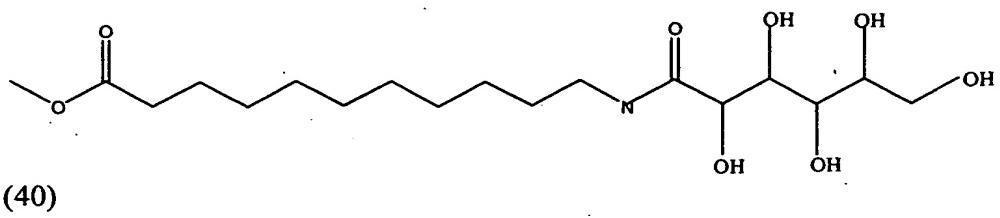
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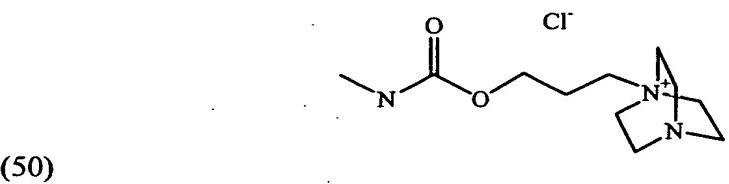
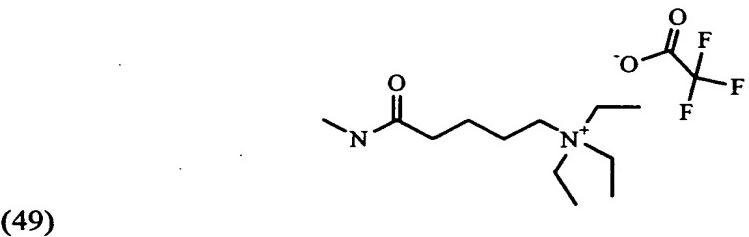
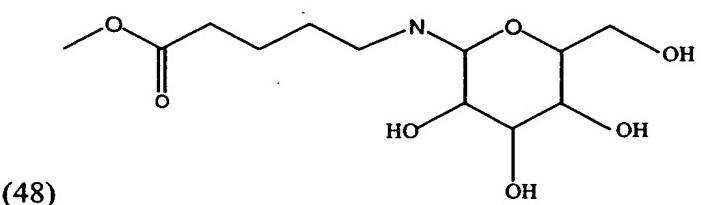
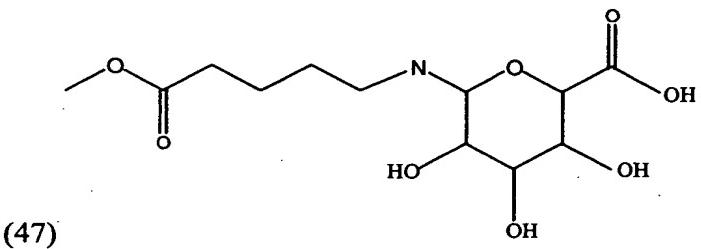
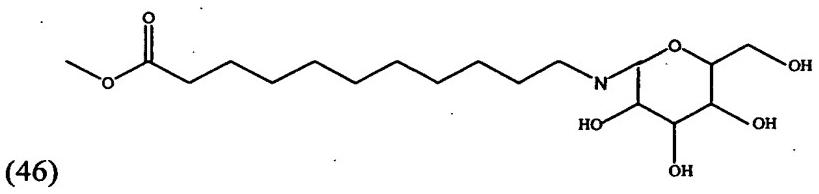
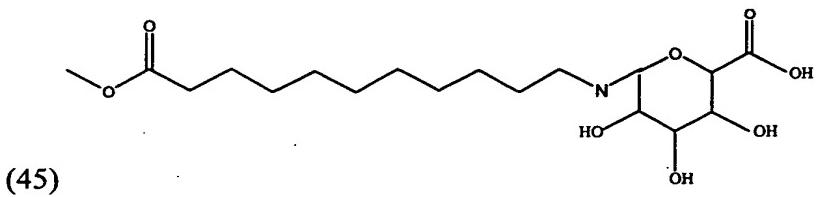


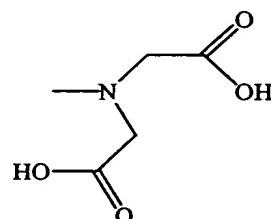
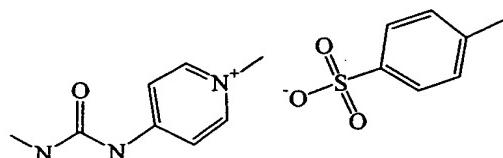
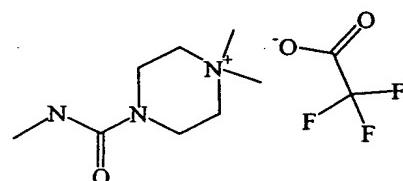
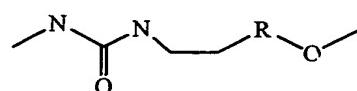
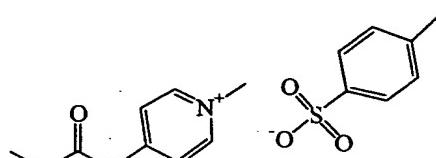
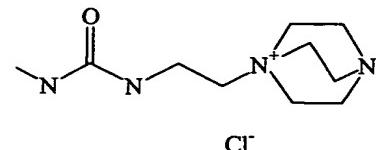
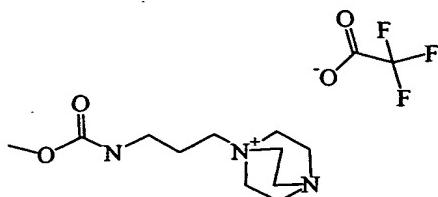
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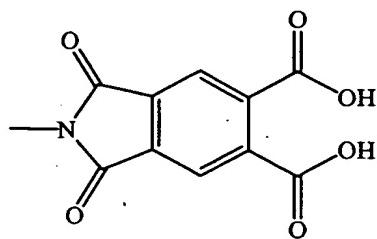


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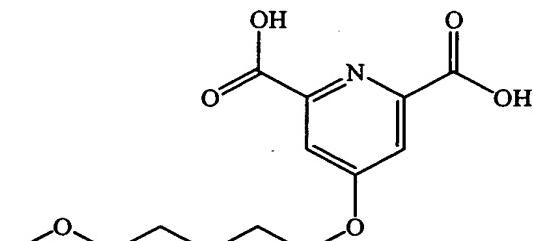




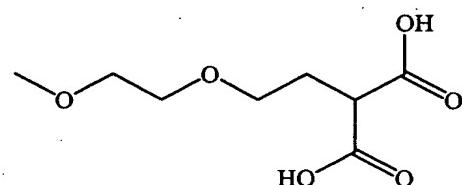




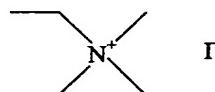
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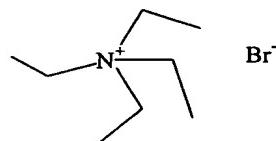
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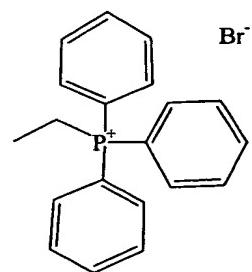
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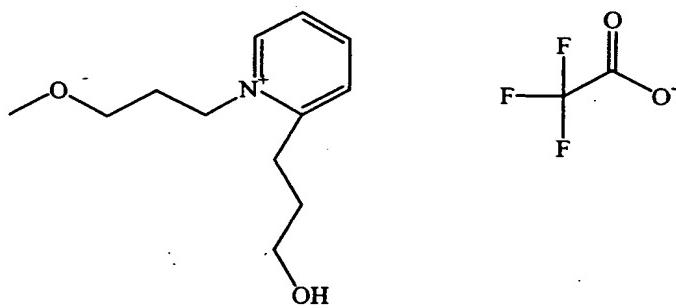
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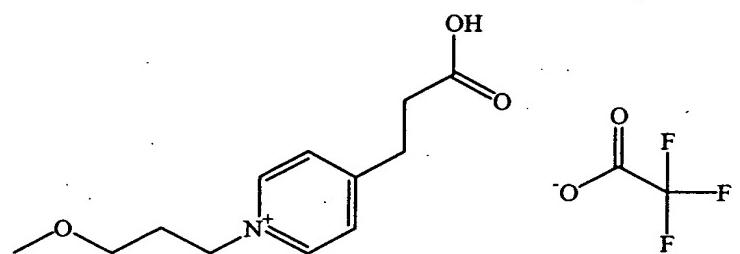
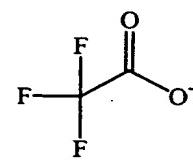
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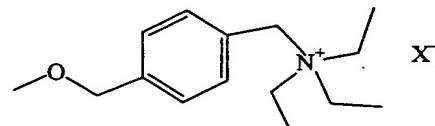
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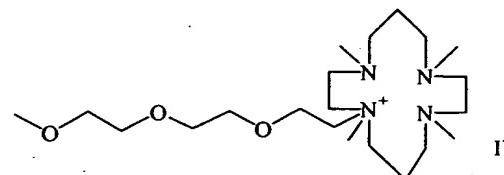
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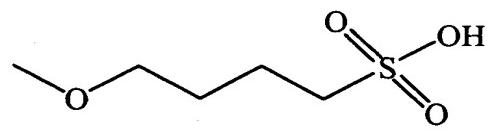
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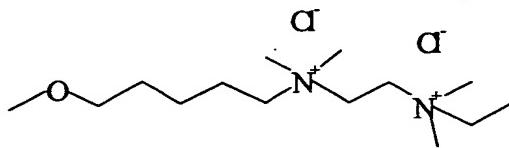
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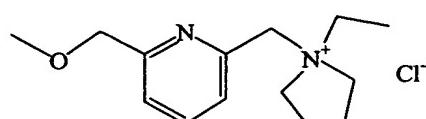
(67)



(68)



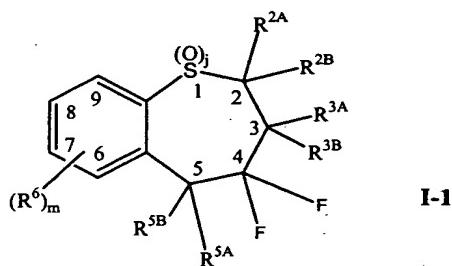
(69) and



(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

[527] 63. A method of forming a compound of the Formula I-1:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A}, R^{3B}, R^{5A}, and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl-R⁵; -OR⁹; -NR⁹R¹⁰; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein R⁹ and R¹⁰ are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R⁵ is selected from the group consisting of hydrogen; hydrocarbyl; heterocyclyl; quaternary heterocyclyl; -OR⁹; -SR⁹; -S(O)R⁹; -SO₂R⁹; and -SO₃R⁹;

wherein when R⁵ is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with -NH-X-R or -O-X-R;

wherein X is selected from the group consisting of -(C=O)_s-alkyl-; -(C=O)_s-alkyl-NH-;-(C=O)_s-alkyl-O-; -(C=O)_s-alkyl-(C=O)_t; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R⁹ and R¹⁰ are as previously defined;

wherein, when R⁵ ≠ H, R⁵ is optionally substituted with one or more radicals independently selected from the group consisting of halogen; -NO₂; -CN; oxo; hydrocarbyl; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -SO₂R¹³; -SO₃R¹³; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -CO₂R¹³; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -C(O)NR¹³R¹⁴; -C(O)OM; -COR¹³; -NR¹³C(O)R¹⁴; -NR¹³C(O)NR¹⁴R¹⁵; -NR¹³CO₂R¹⁴; -OC(O)R¹³; -OC(O)NR¹³R¹⁴; -NR¹³SOR¹⁴; -NR¹³SO₂R¹⁴; -NR¹³SONR¹⁴R¹⁵; -NR¹³SO₂NR¹⁴R¹⁵; -PR¹³R¹⁴; -P(O)R¹³R¹⁴; -P⁺R¹³R¹⁴R¹⁵A⁻; -P(OR¹³)OR¹⁴; -S⁺R¹³R¹⁴A⁻; and -N⁺R¹³R¹⁴R¹⁵A⁻;

wherein R¹³, R¹⁴, and R¹⁵ are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A⁻ is a pharmaceutically acceptable anion;

wherein M is a pharmaceutically acceptable cation;

wherein one or more R⁶ radicals are independently selected from the group consisting of hydrogen; halogen; -CN; -NO₂; hydrocarbyl; -R⁵; -OR¹³; -NR¹³R¹⁴; -SR¹³; -S(O)R¹³; -S(O)₂R¹³; -SO₃R¹³; -S⁺R¹³R¹⁴A⁻; -NR¹³OR¹⁴; -NR¹³NR¹⁴R¹⁵; -OM; -SO₂OM; -SO₂NR¹³R¹⁴; -NR¹⁴C(O)R¹³; -C(O)OM; -

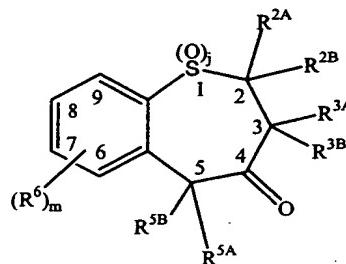
$\text{S(O)NR}^{13}\text{R}^{14}$; $-\text{N}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; $-\text{PR}^{13}\text{R}^{14}$; $-\text{P(O)R}^{13}\text{R}^{14}$; $-\text{P}^+\text{R}^{13}\text{R}^{14}\text{R}^{15}\text{A}^-$; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

wherein R^{13} , R^{14} , R^{15} , A^- , and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof,

said method comprising the steps of:

- (a) forming a compound of Formula S1-78c:



S1-78c

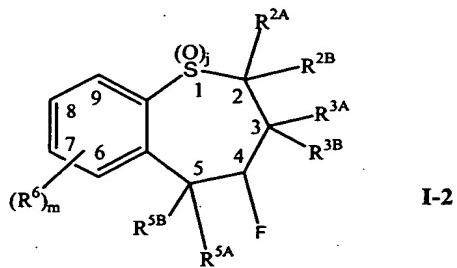
wherein $\text{R}^{2\text{A}}$, $\text{R}^{2\text{B}}$, $\text{R}^{3\text{A}}$, $\text{R}^{3\text{B}}$, $\text{R}^{5\text{A}}$, $\text{R}^{5\text{B}}$, R^6 , m and j are as previously defined; and

- (b) treating said compound of Formula S1-78c with diethylaminosulfur trifluoride to form said compound of Formula I-1.

[528] 64. The method of embodiment 63 wherein said treating step (b) is carried out in an inert solvent.

[529] 65. The method of embodiment 64 wherein said treating step (b) is carried out in said inert solvent cooled to from about -50°C to about -78°C .

[530] 66. A method of forming a compound of Formula I-2:



or a pharmaceutically acceptable salt, solvate, or prodrug thereof

wherein j is 0, 1 or 2;

wherein m is 0, 1, 2, 3 or 4;

wherein R^{2A} and R^{2B} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein R^{3A} , R^{3B} , R^{5A} , and R^{5B} are independently selected from the group consisting of hydrogen, alkyl; cycloalkyl; alkenyl; alkynyl; heterocyclyl; quaternary heterocyclyl, oxo; aryl- R^5 ; - OR^9 ; - NR^9R^{10} ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein R^9 and R^{10} are independently selected from the group consisting of hydrogen; hydrocarbyl; amino; and hydrocarbylamino;

wherein R^5 is selected from the group consisting of hydrogen; hydrocarbyl; heterocyclyl; quaternary heterocyclyl; - OR^9 ; - SR^9 ; - $S(O)R^9$; - SO_2R^9 ; and - SO_3R^9 ;

wherein when R^5 is said cycloalkyl, aryl or heterocyclyl, said cycloalkyl, aryl or heterocyclyl are optionally substituted with - $NH-X-R$ or - $O-X-R$;

wherein X is selected from the group consisting of -($C=O)_s$ -alkyl-; -($C=O)_s$ -alkyl-NH-; -($C=O)_s$ -alkyl-O-; -($C=O)_s$ -alkyl-($C=O)_t$; and a covalent bond, wherein s and t are independently 0 or 1;

wherein R is selected from the group consisting of monosaccharides, disaccharides, and polysaccharides, wherein said monosaccharides, disaccharides, and polysaccharides are optionally protected with one or more sugar protecting groups;

wherein R^9 and R^{10} are as previously defined;

wherein, when $R^5 \neq H$, R^5 is optionally substituted with one or more radicals independently selected from the group consisting of halogen; $-NO_2$; $-CN$; oxo; hydrocarbyl; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-SO_2R^{13}$; $-SO_3R^{13}$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-CO_2R^{13}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-C(O)NR^{13}R^{14}$; $-C(O)OM$; $-COR^{13}$; $-NR^{13}C(O)R^{14}$; $-NR^{13}C(O)NR^{14}R^{15}$; $-NR^{13}CO_2R^{14}$; $-OC(O)R^{13}$; $-OC(O)NR^{13}R^{14}$; $-NR^{13}SOR^{14}$; $-NR^{13}SO_2R^{14}$; $-NR^{13}SONR^{14}R^{15}$; $-NR^{13}SO_2NR^{14}R^{15}$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; $-P(OR^{13})OR^{14}$; $-S^+R^{13}R^{14}A^-$; and $-N^+R^{13}R^{14}R^{15}A^-$;

wherein R^{13} , R^{14} , and R^{15} are independently selected from the group consisting of hydrogen and hydrocarbyl;

wherein A^- is a pharmaceutically acceptable anion;

wherein M is a pharmaceutically acceptable cation;

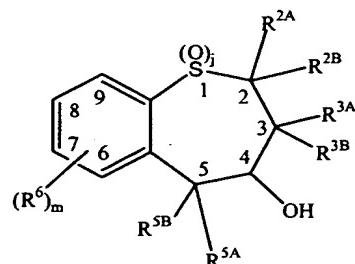
wherein one or more R^6 radicals are independently selected from the group consisting of hydrogen; halogen; $-CN$; $-NO_2$; hydrocarbyl; $-R^5$; $-OR^{13}$; $-NR^{13}R^{14}$; $-SR^{13}$; $-S(O)R^{13}$; $-S(O)_2R^{13}$; $-SO_3R^{13}$; $-S^+R^{13}R^{14}A^-$; $-NR^{13}OR^{14}$; $-NR^{13}NR^{14}R^{15}$; $-OM$; $-SO_2OM$; $-SO_2NR^{13}R^{14}$; $-NR^{14}C(O)R^{13}$; $-C(O)OM$; $-S(O)NR^{13}R^{14}$; $-N^+R^{13}R^{14}R^{15}A^-$; $-PR^{13}R^{14}$; $-P(O)R^{13}R^{14}$; $-P^+R^{13}R^{14}R^{15}A^-$; amino acid residue; peptide residue; polypeptide residue; and carbohydrate residue;

wherein R^{13} , R^{14} , R^{15} , A^- , and M are as defined above; and

wherein, in each instance, said hydrocarbyl may be optionally substituted with one or more groups comprising one or more heteroatoms, and wherein, in each instance, said hydrocarbyl optionally may have one or more carbon atoms replaced by one or more heteroatoms independently selected from the group consisting of oxygen, nitrogen, sulfur, phosphorus and combinations thereof,

said method comprising the steps of:

(a) forming a compound of Formula S1-78a:



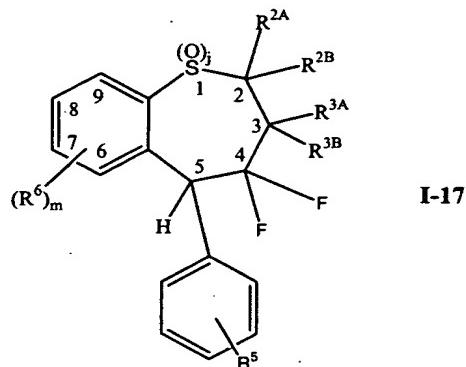
wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined; and

- (b) treating said compound of Formula S1-78a with diethylaminosulfur trifluoride to form said compound of Formula I-2.

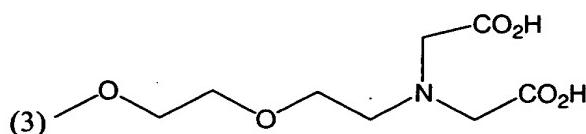
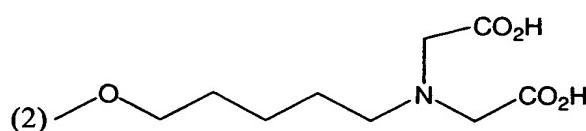
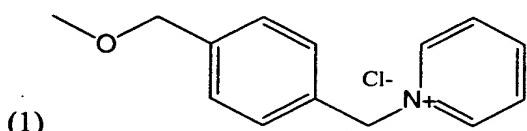
[531] 67. The method of embodiment 66 wherein said treating step (b) is carried out in an inert solvent.

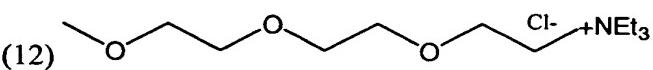
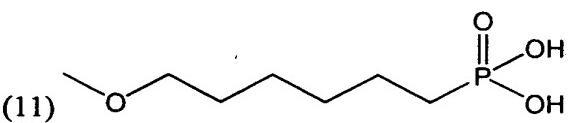
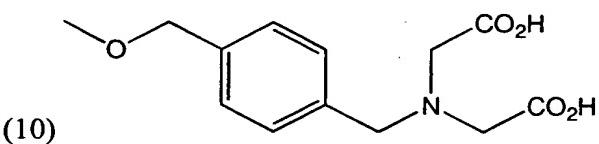
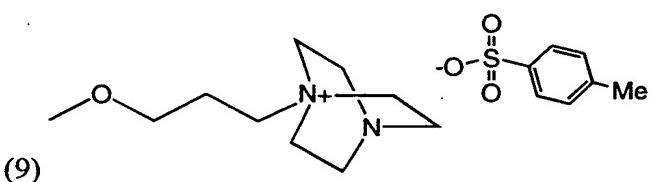
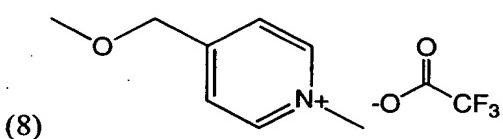
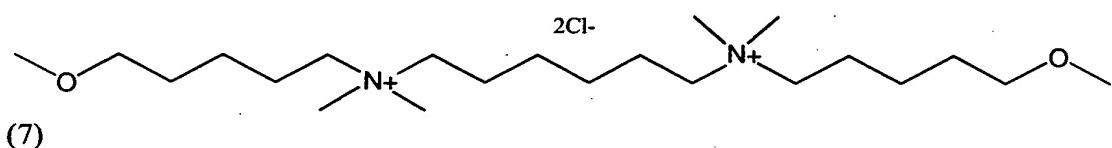
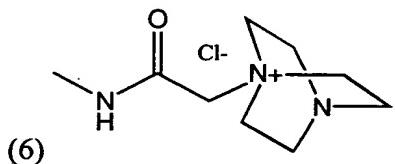
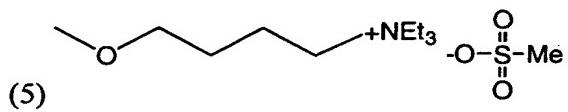
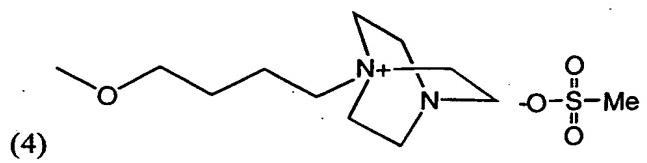
[532] 68. The method of embodiment 67 wherein said treating step (b) is carried out in said inert solvent cooled to from about -50 °C to about -78 °C.

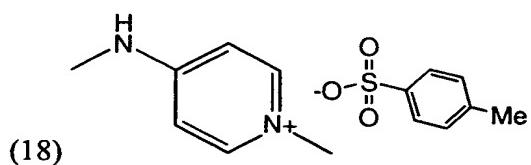
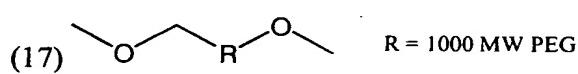
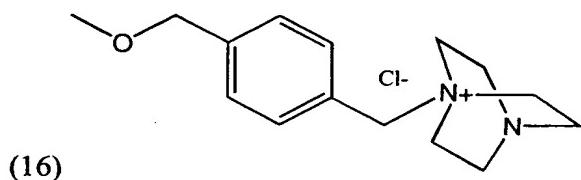
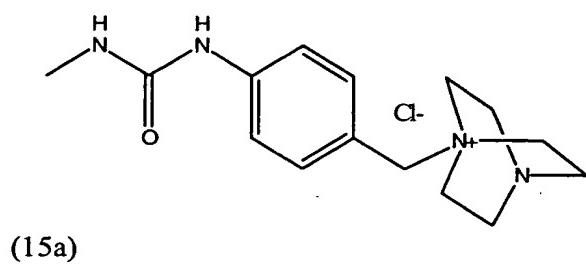
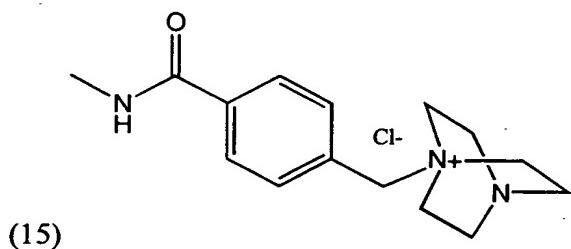
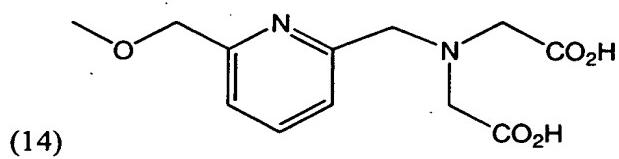
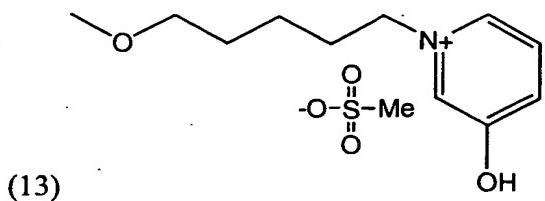
[533] 69. The method of embodiment 63 wherein said compound of Formula I-1 comprises Formula I-17 represented by:

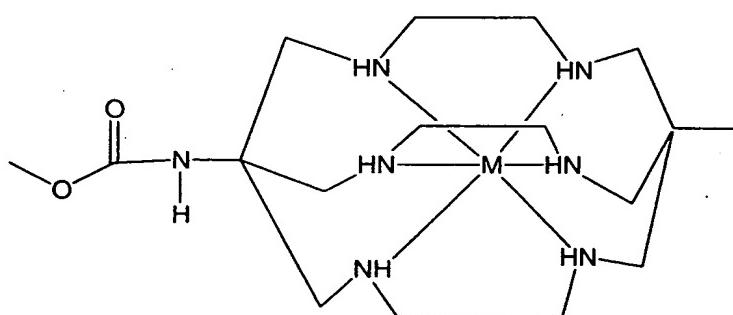
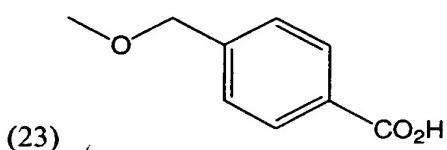
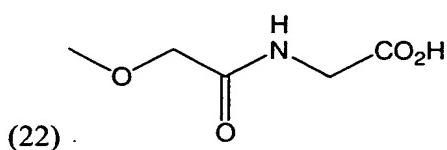
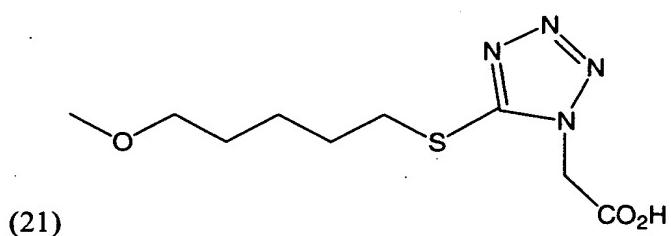
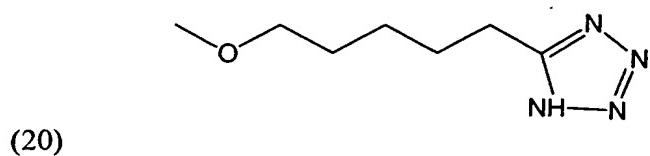
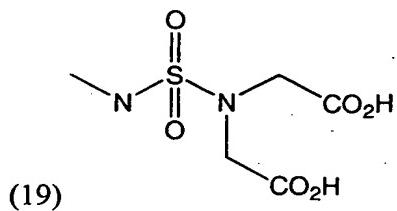


wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined and R^5 is selected from the group consisting of (1) - (69) and (70):

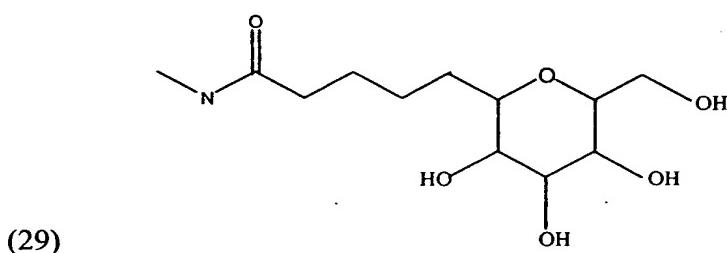
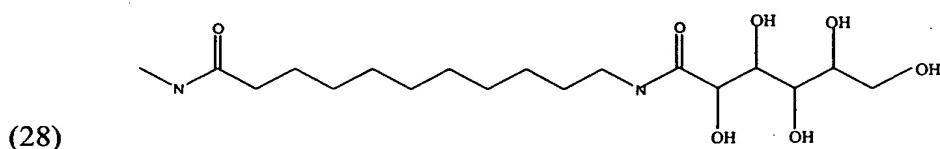
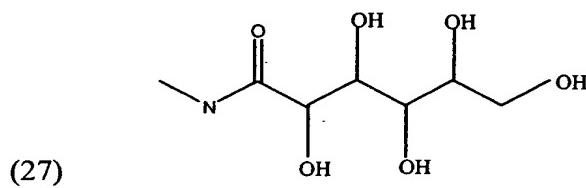
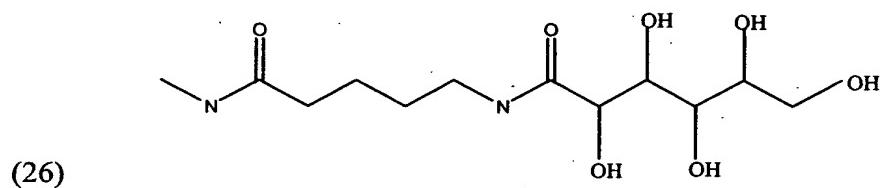
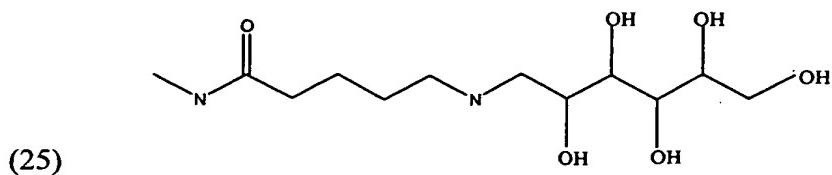


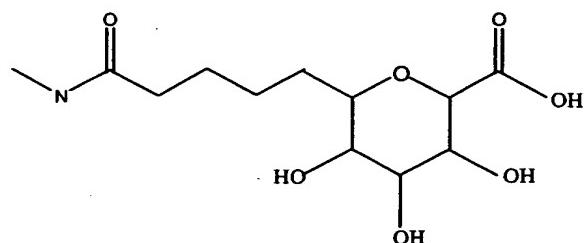




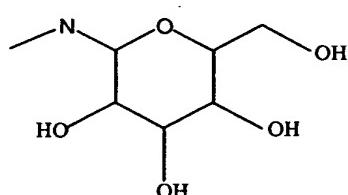


(24) $M = \text{Co}^{\text{II}}, \text{III}, \text{Mn}^{\text{II}}, \text{III}, \text{Fe}^{\text{II}}, \text{III}, \text{Ni}^{\text{II}}, \text{III},$
 $\text{Cr}^{\text{III}}, \text{Cu}^{\text{II}}, \text{Zn}^{\text{II}}, \text{Cd}^{\text{II}}, \text{Ga}^{\text{III}}, \text{In}^{\text{III}}, \text{V}^{\text{IV}},$
 $\text{Ru}^{\text{II}}, \text{Pr}^{\text{IV}}, \text{Rh}^{\text{III}} \text{ or Ir}^{\text{III}}$

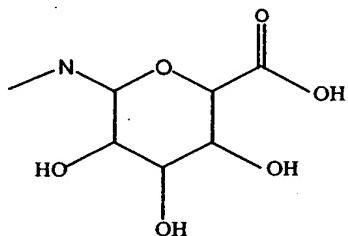




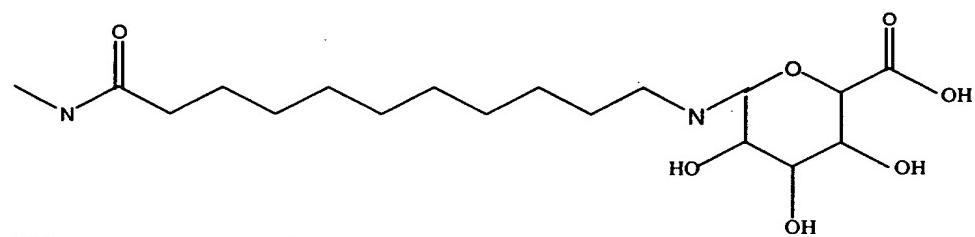
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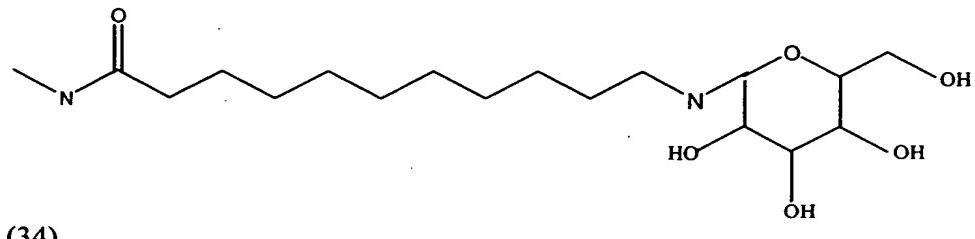
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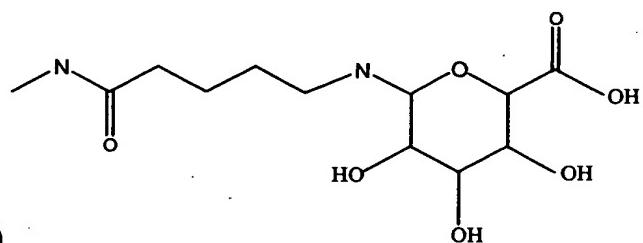
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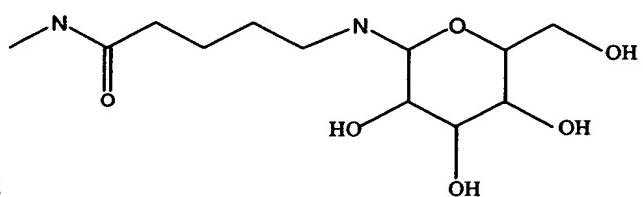
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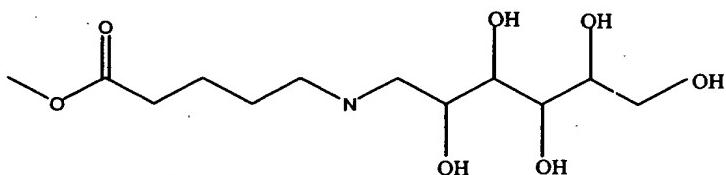
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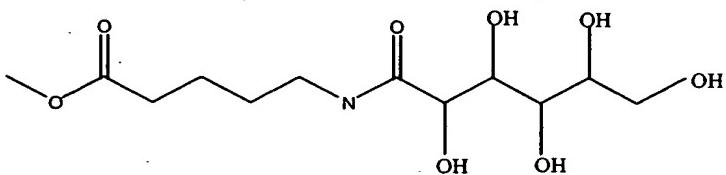
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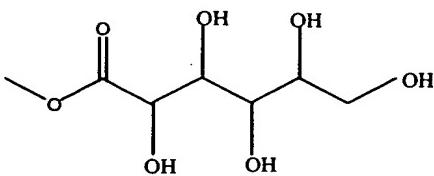
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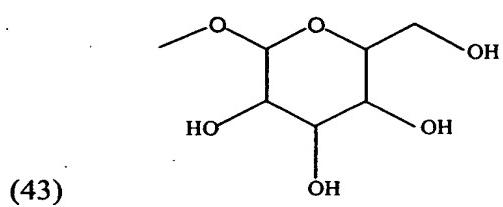
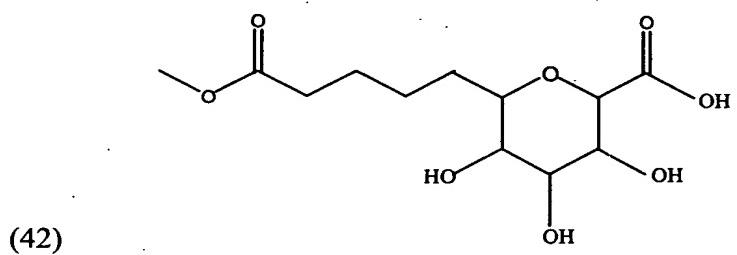
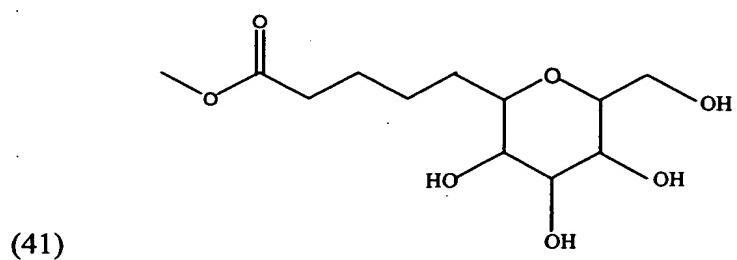
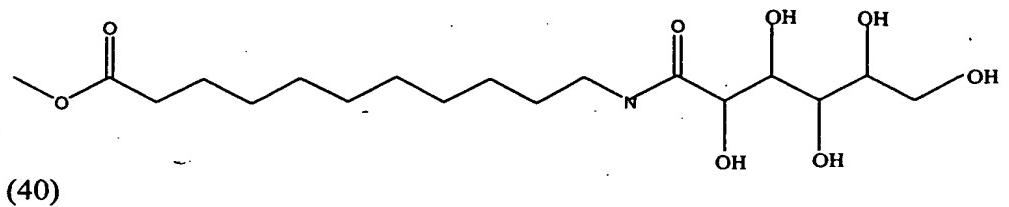
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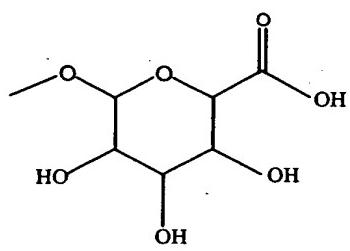


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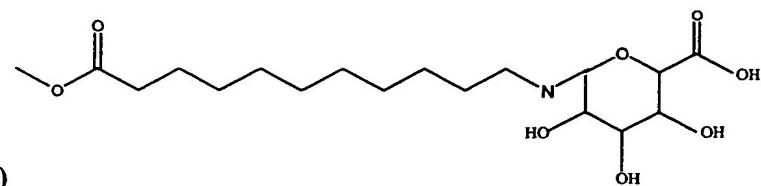


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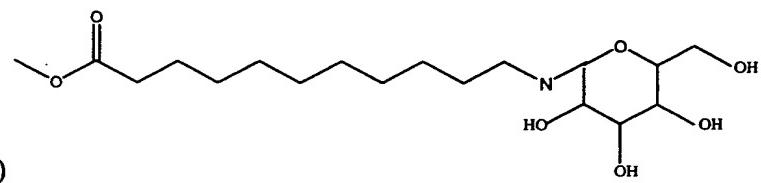




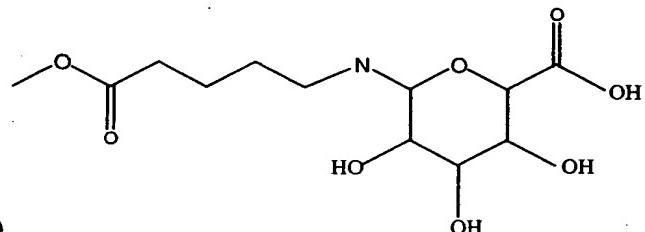
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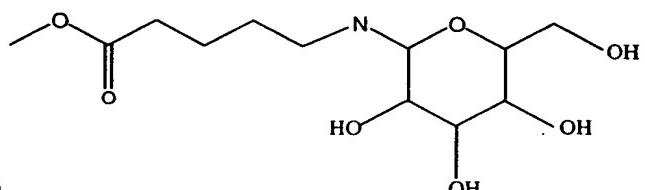
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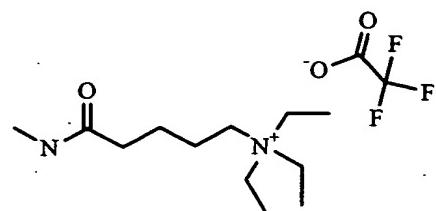
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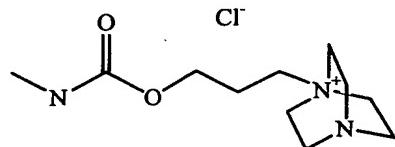
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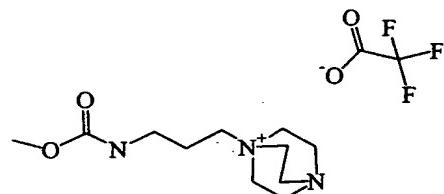
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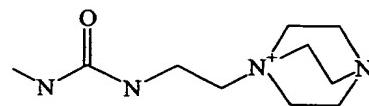
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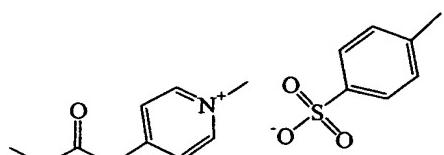
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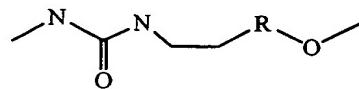
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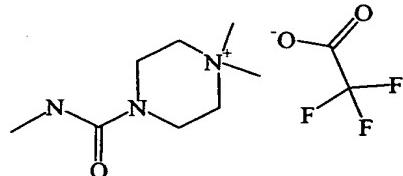
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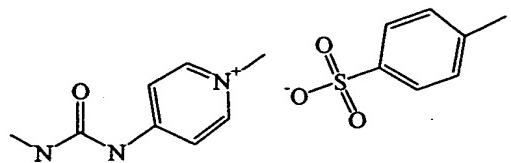
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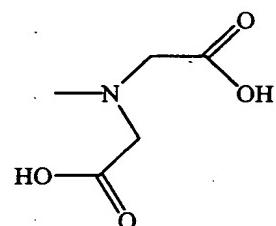
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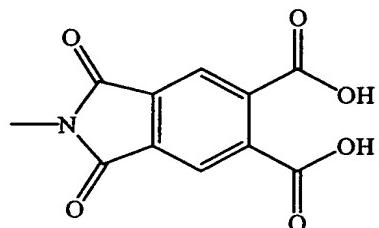
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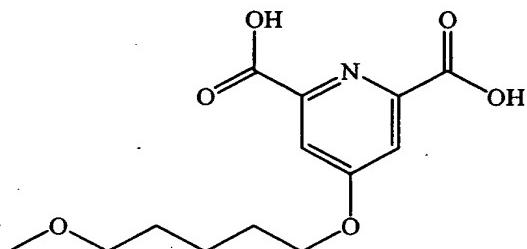
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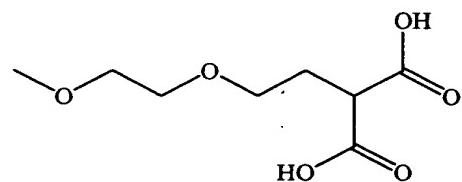
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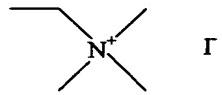
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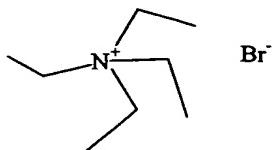
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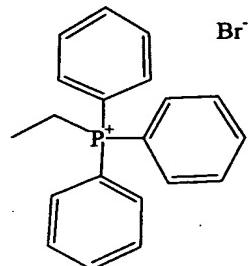
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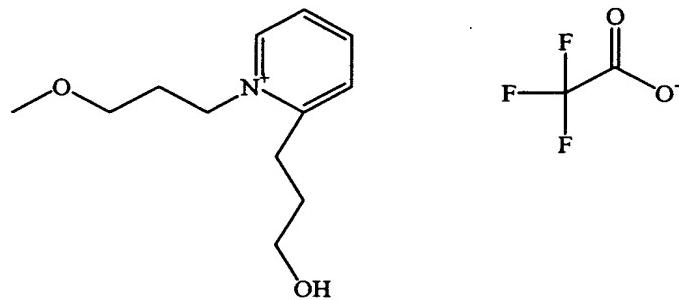
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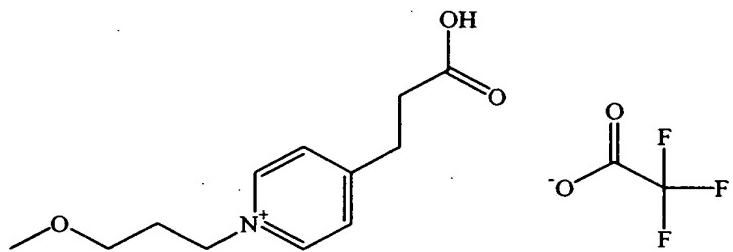
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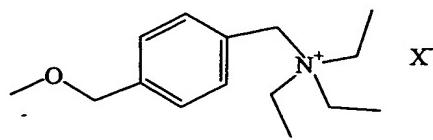
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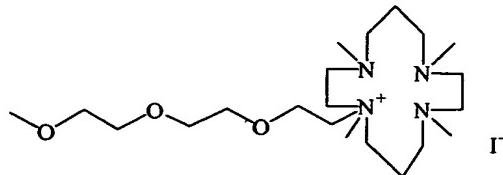
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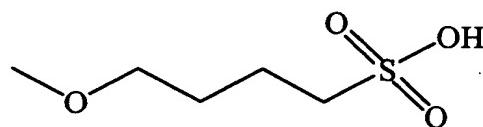
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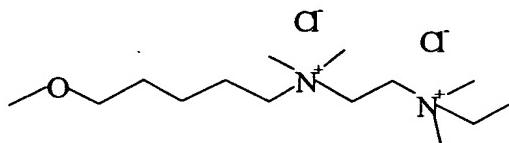
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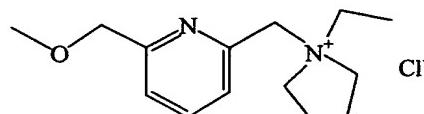
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(68)



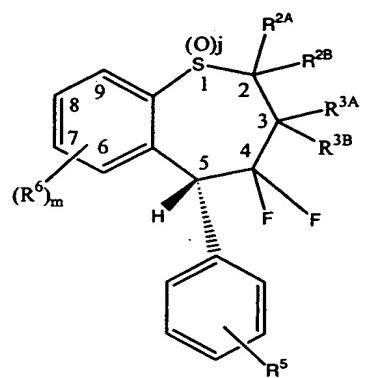
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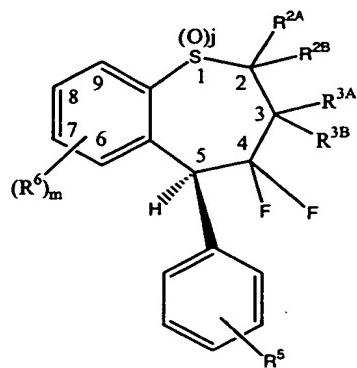
(70)

provided that when said R^5 is (7), (17) or (24), then said R^{5A} is a left end of said R^5 and said R^{5B} is a right end of said R^5 or vice versa.

[534] 70. The method of embodiment 69 wherein said Formula I-17 comprises Formulas I-21 or I-22 represented by:

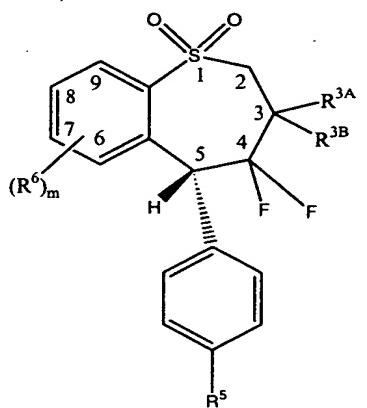


I-21

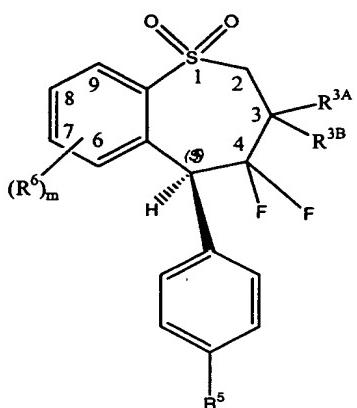


I-22.

[535] 71. The method of embodiment 70 wherein said Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:



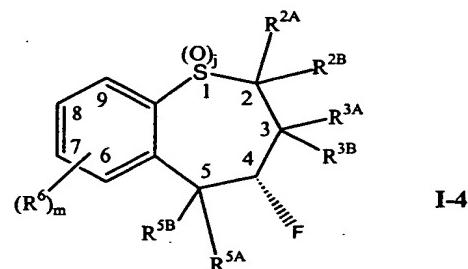
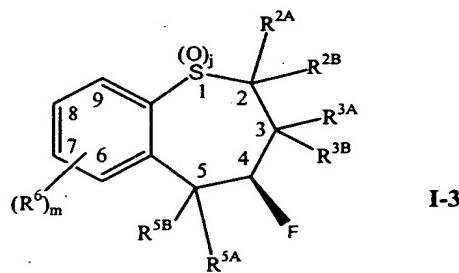
I-9



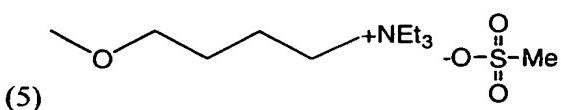
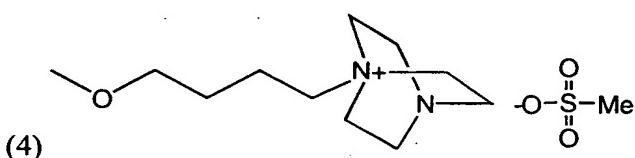
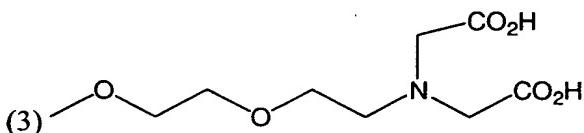
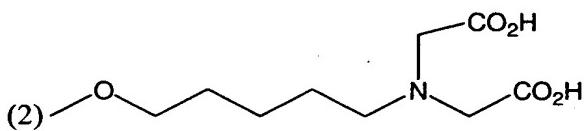
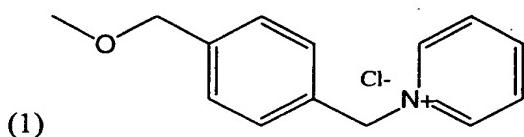
I-10.

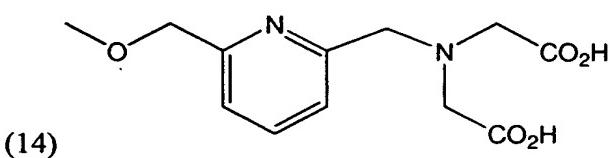
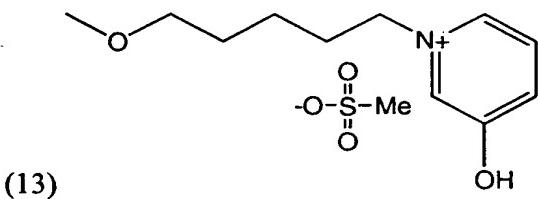
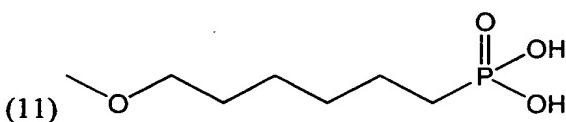
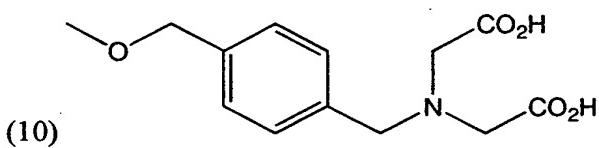
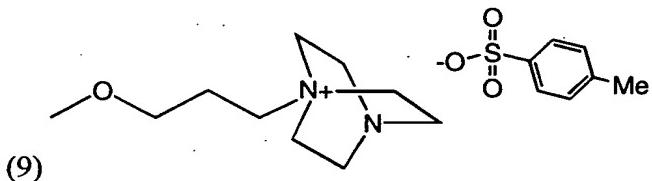
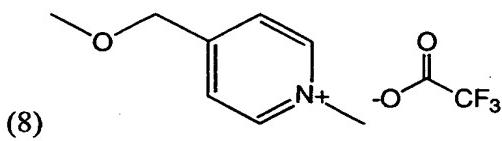
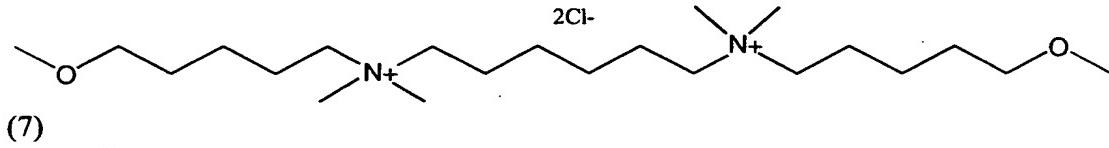
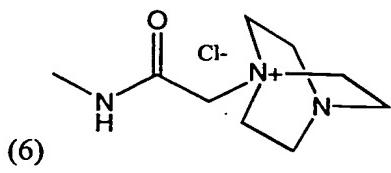
[536] 72. The method of embodiment 70 wherein said R⁵ group is attached at least either at a meta position or at a para position of said phenyl ring attached to said 5-carbon position of said benzothiepene of said Formulas I-21 or I-22.

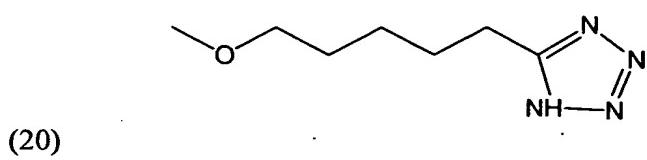
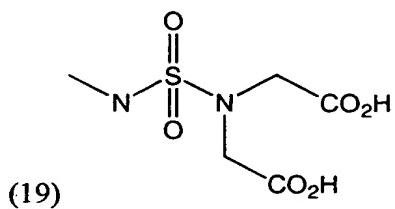
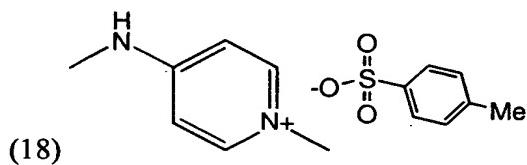
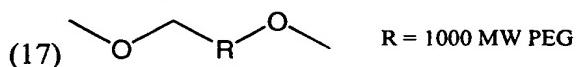
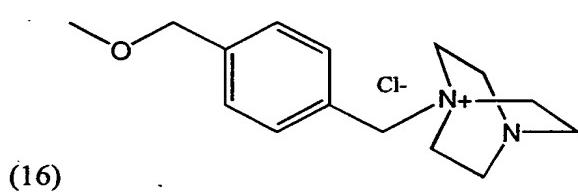
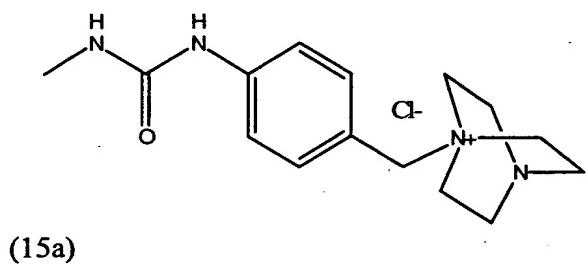
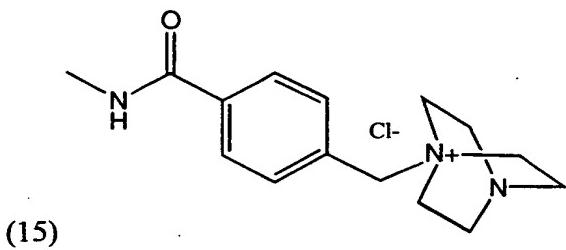
[537] 73. The method of embodiment 66 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-3 and I-4 represented by:

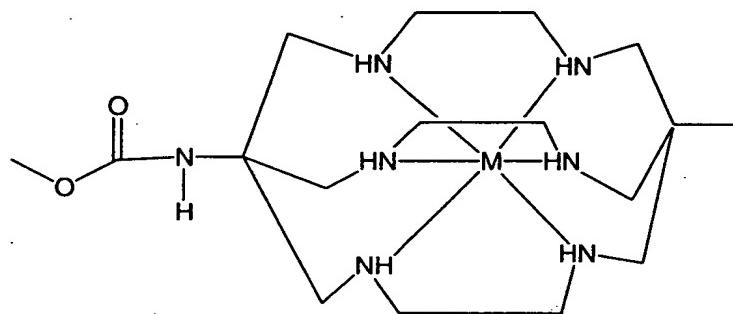
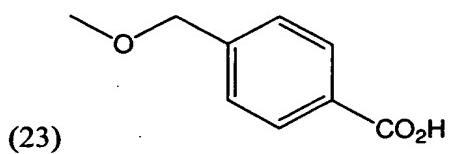
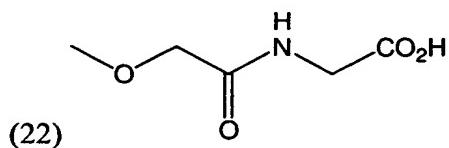
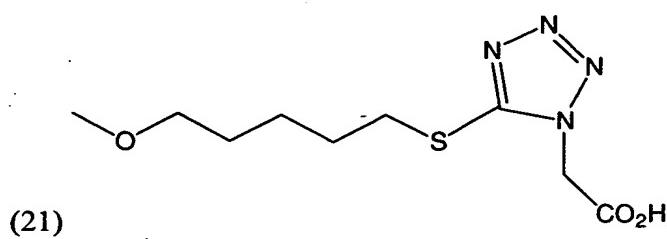


wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined and said R^5 is selected from the group consisting of (1) - (69) and (70):

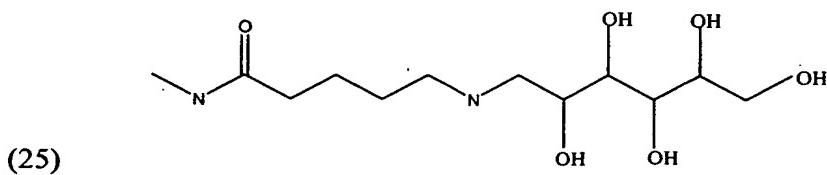


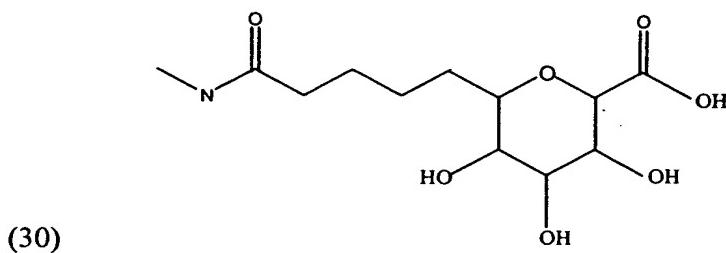
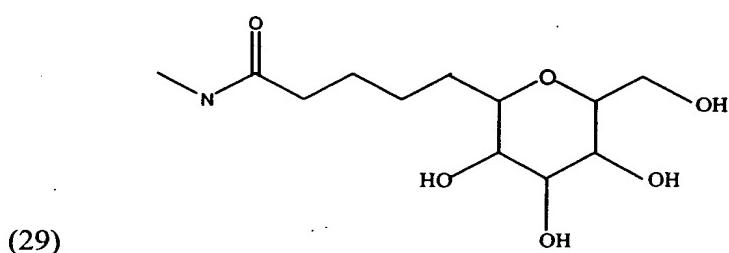
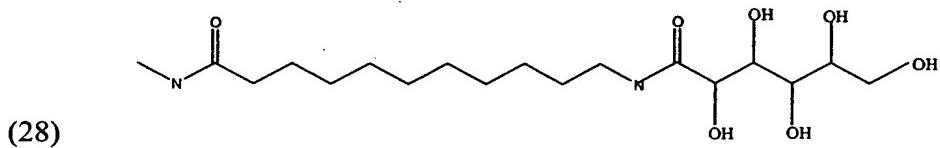
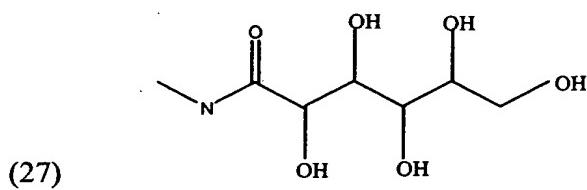
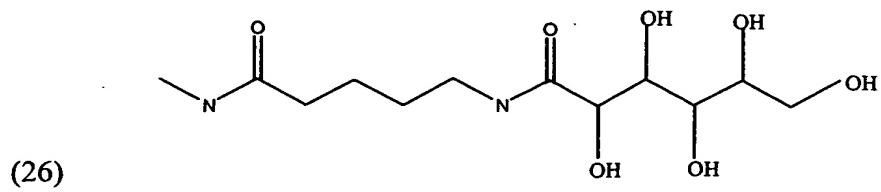


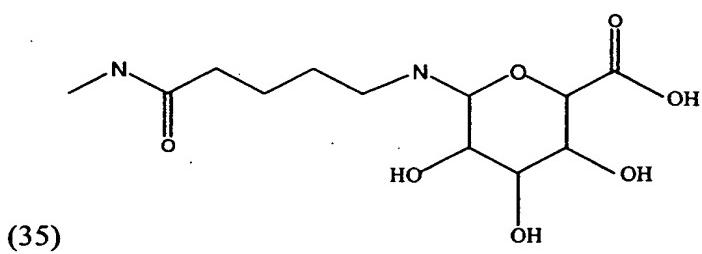
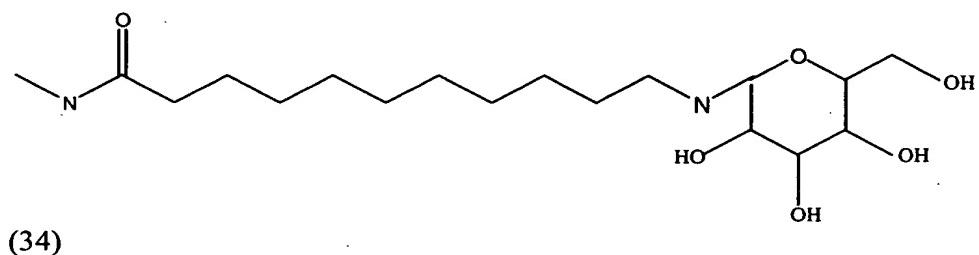
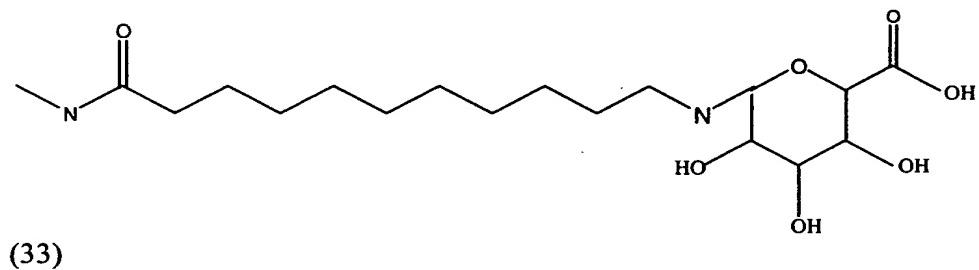
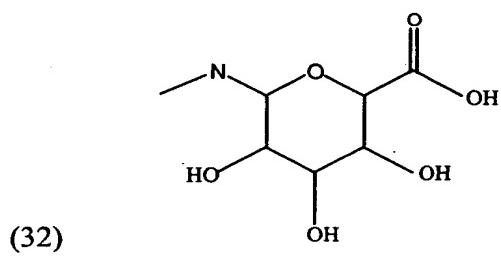
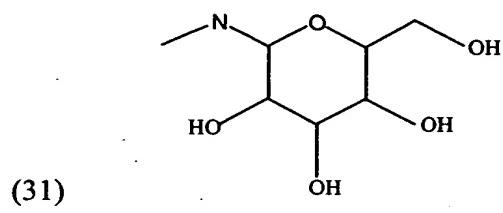


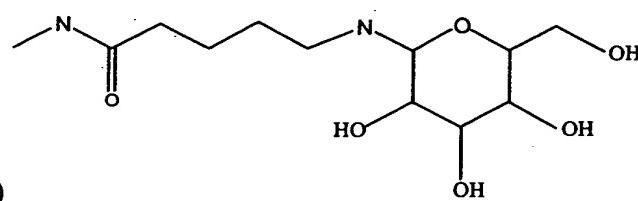


(24) $M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}

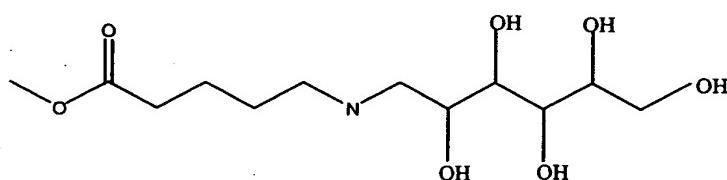




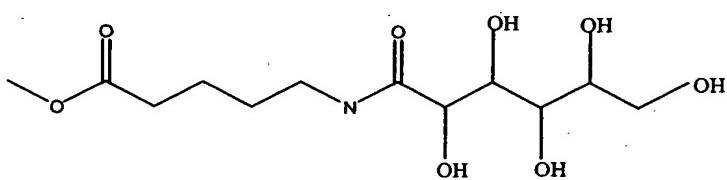




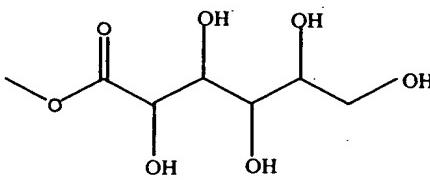
(36)



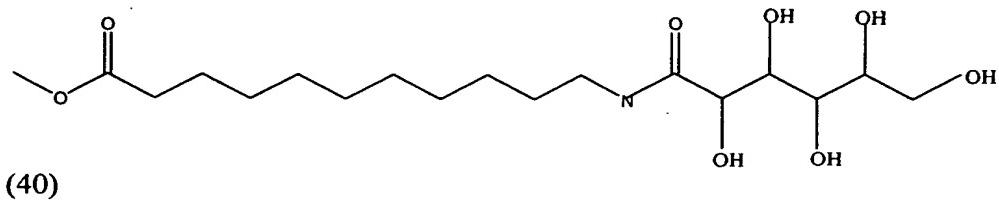
(37)



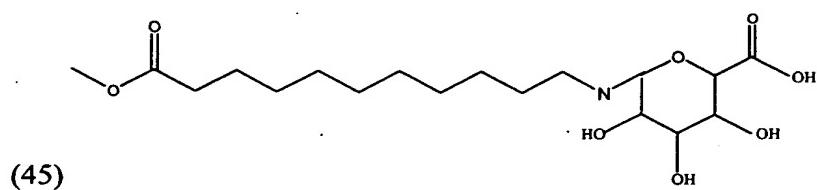
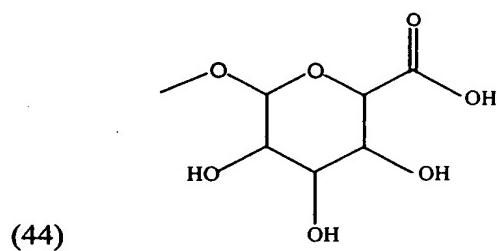
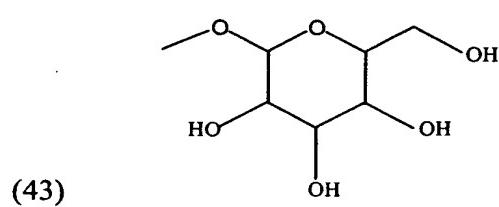
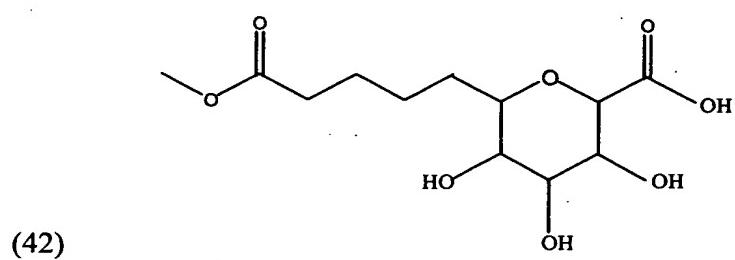
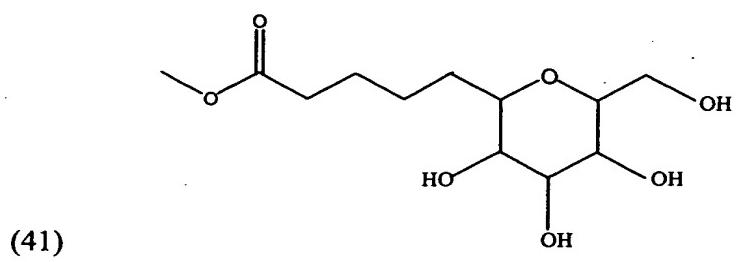
(38)

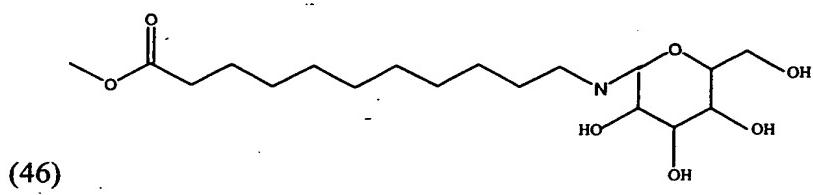


(39)

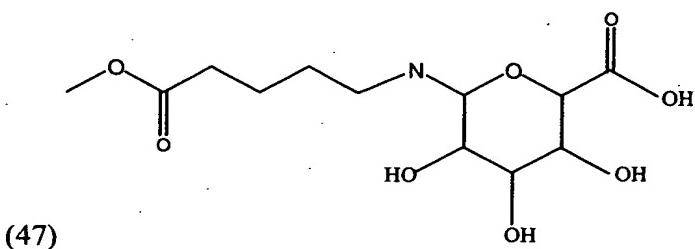


(40)

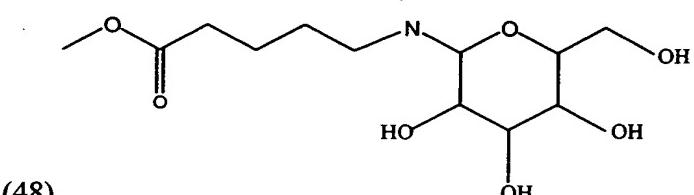




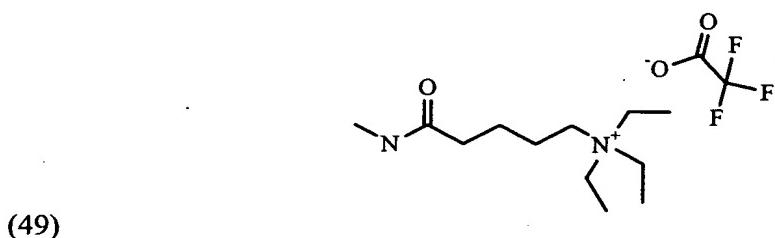
(46)



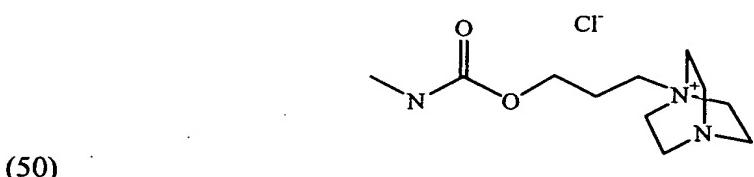
(47)



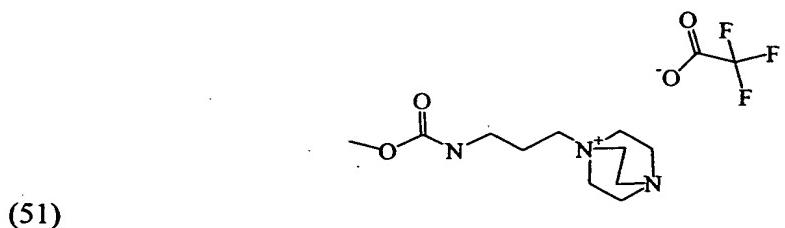
(48)



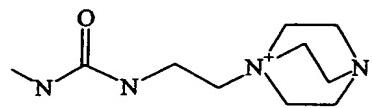
(49)



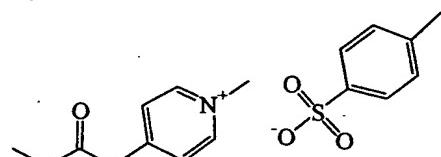
(50)



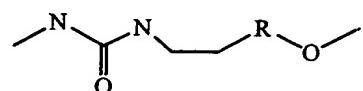
(51)



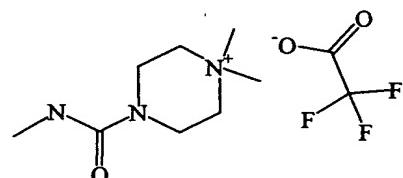
(52)



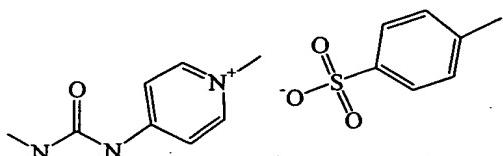
(53)



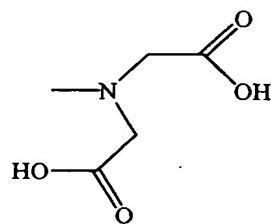
(54)



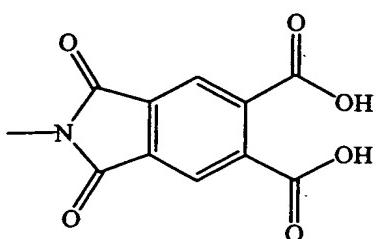
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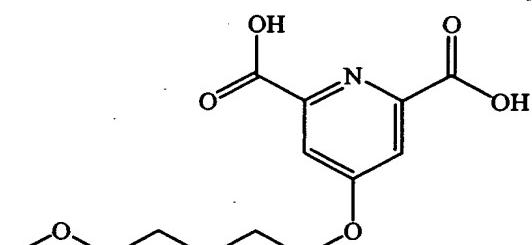
(56)



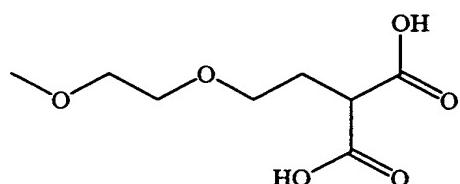
(57)



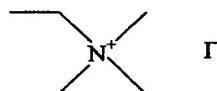
(58)



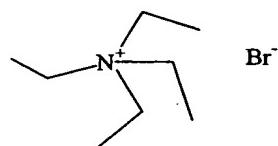
(59)



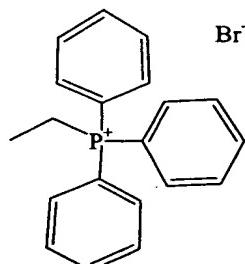
(60)



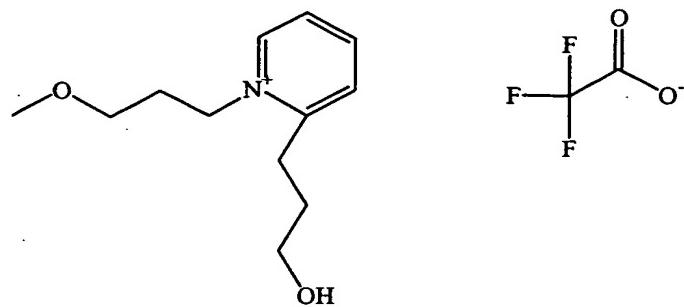
(61)



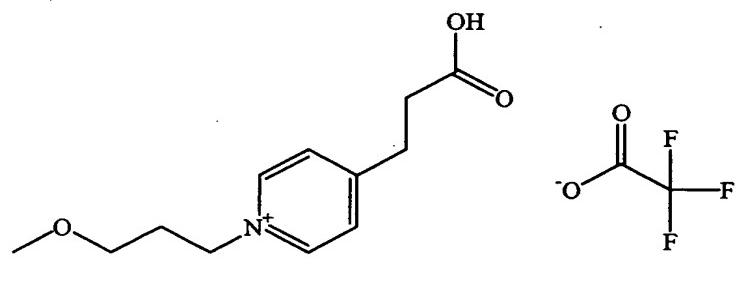
(62)



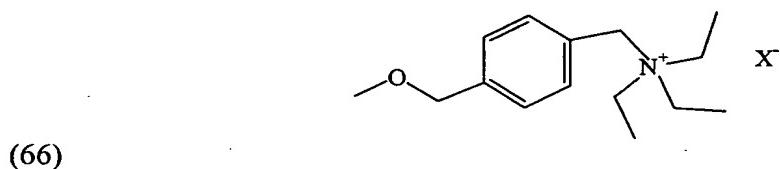
(63)



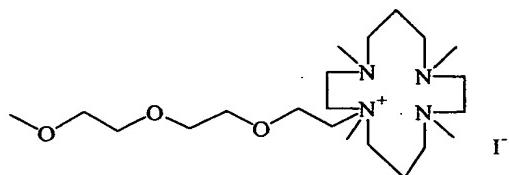
(64)



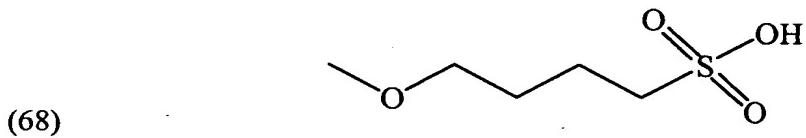
(65)



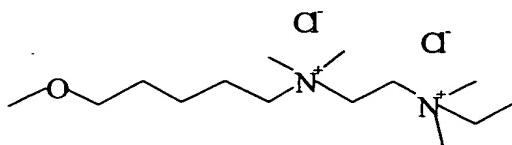
(66)



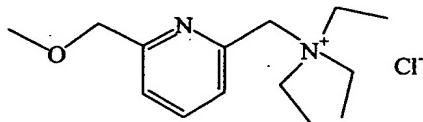
(67)



(68)



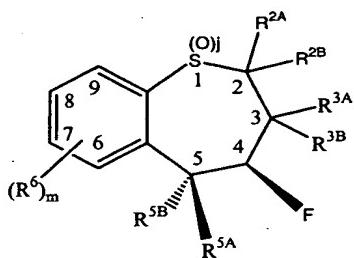
(69) and



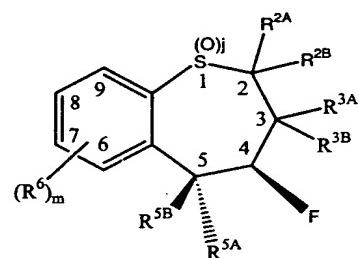
(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

- [538] 74. The method of embodiment 73 wherein said Formula I-3 comprises a member selected from the group consisting of Formulas I-5 and I-6 represented by:

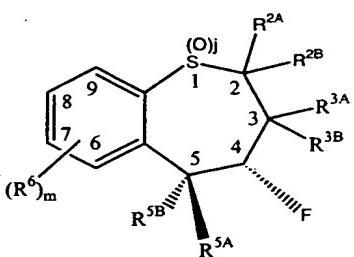


I-5

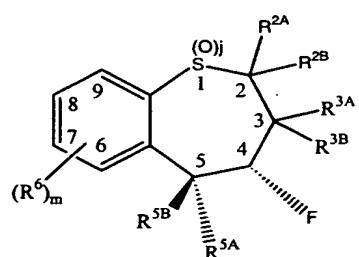


I-6.

- [539] 75. The method of embodiment 73 wherein said Formula I-4 comprises a member selected from the group consisting of Formulas I-7 and I-8 represented by:

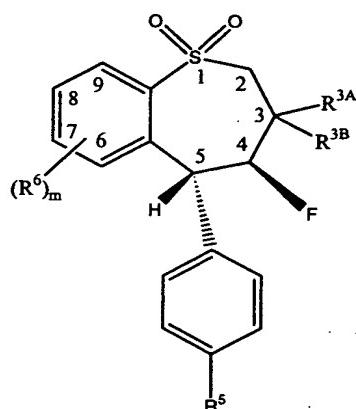


I-7

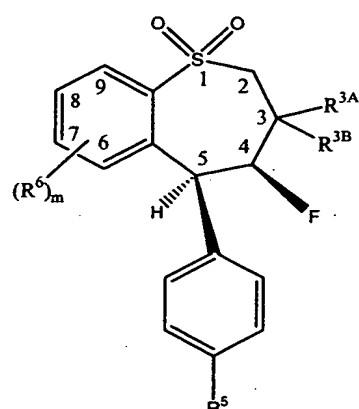


I-8.

[540] 76. The method of embodiment 74 wherein said compounds of Formulas I-6 and I-5 comprise Formulas I-13 and I-14, respectively, represented by:

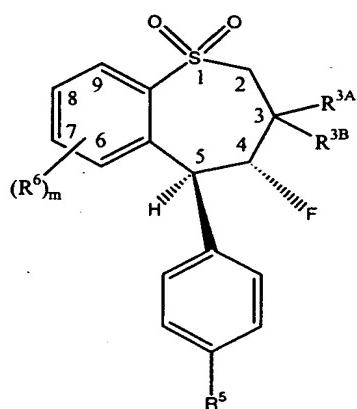


I-13

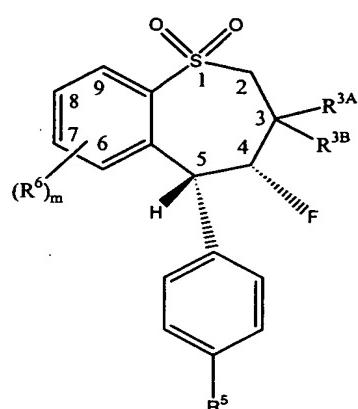


I-14.

[541] 77. The method of embodiment 75 wherein said Formulas I-7 and I-8 comprise Formulas I-15 and I-16, respectively, represented by:

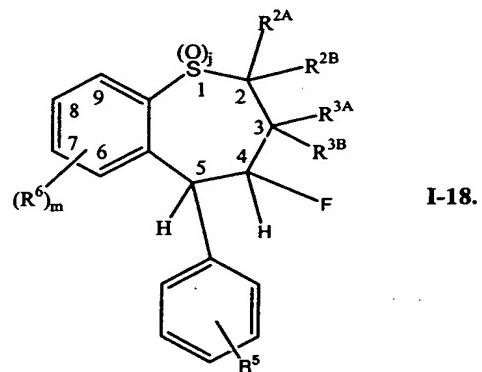


I-15



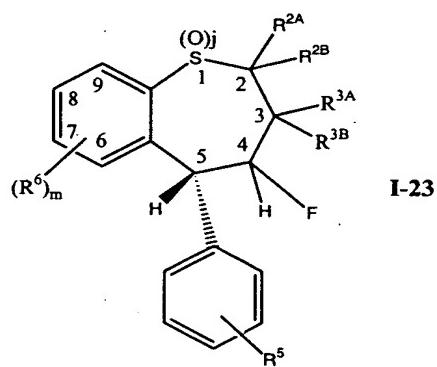
I-16.

[542] 78. The method of embodiment 66 wherein said compound of Formula I-2 comprises a compound of Formula I-18 represented by:

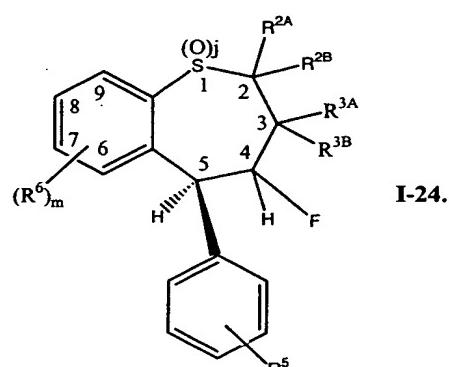


I-18.

[543] 79. The method of embodiment 78 wherein said compound of Formula I-18 comprises a member selected from the group consisting of Formulas I-23 and I-24 represented by:

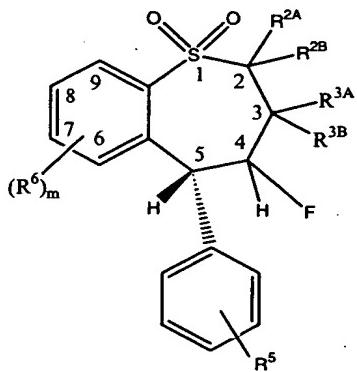


I-23

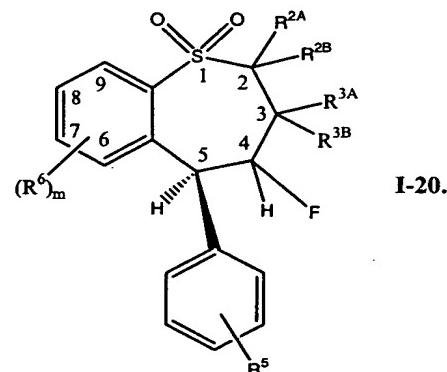


I-24.

[544] 80. The method of embodiment 79 wherein said compounds of Formulas I-23 and I-24 comprises Formulas I-19 and I-20, respectively, represented by:

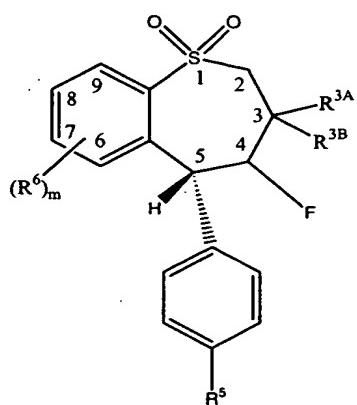


I-19

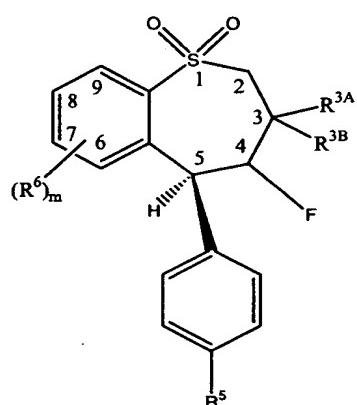


I-20.

[545] 81. The method of embodiment 66 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-11 and I-12, respectively, represented by:

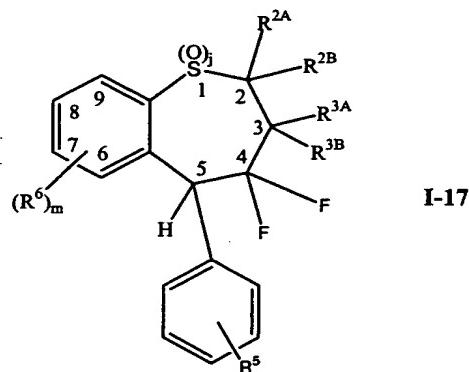


I-11

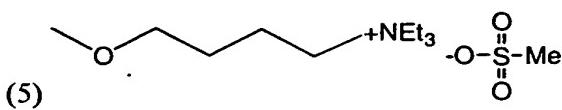
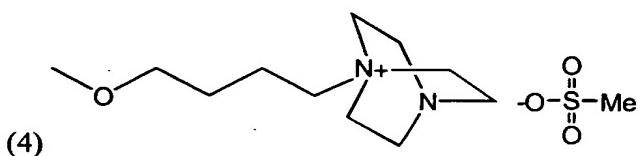
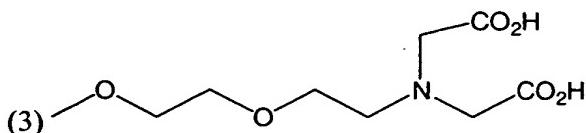
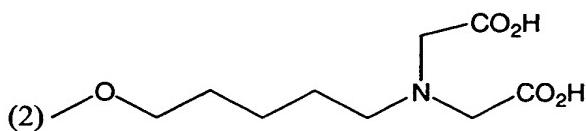
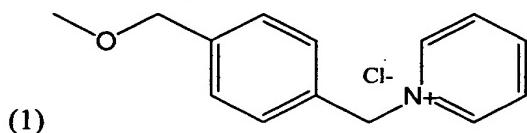


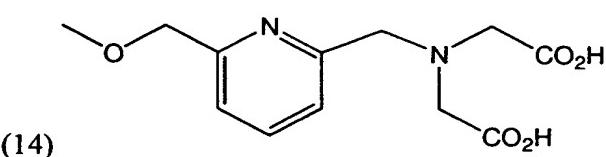
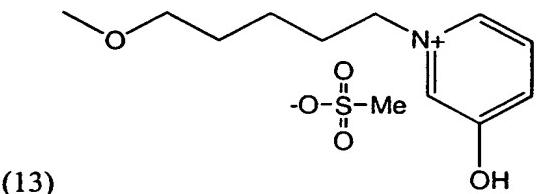
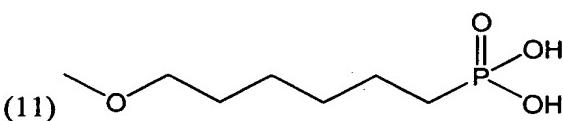
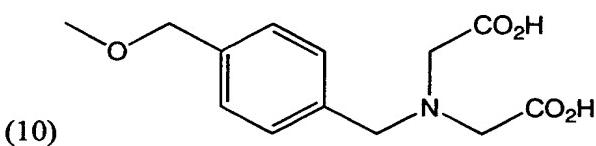
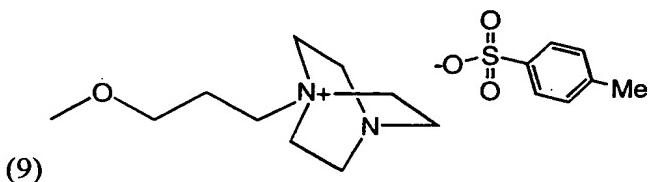
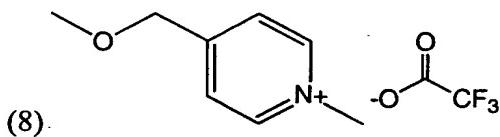
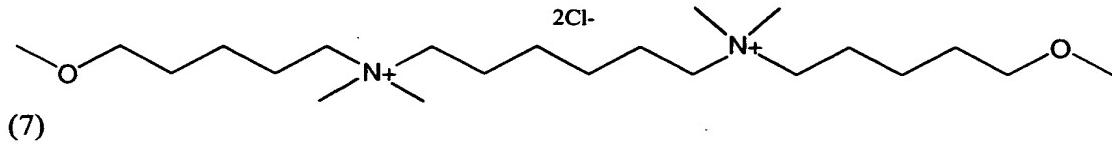
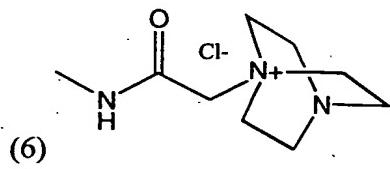
I-12.

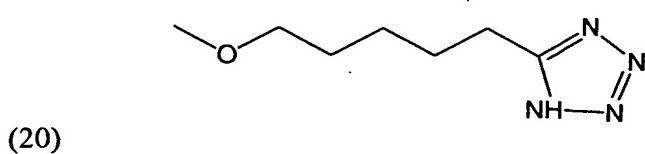
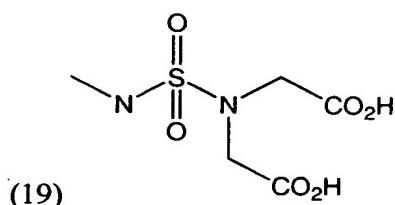
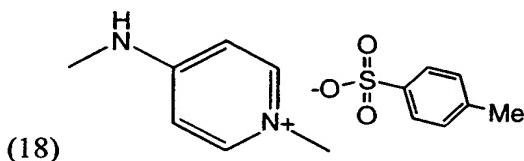
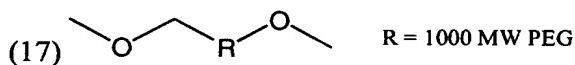
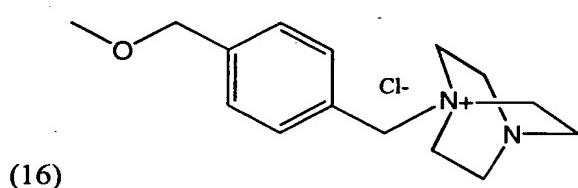
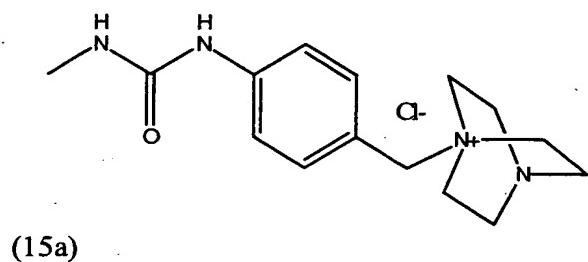
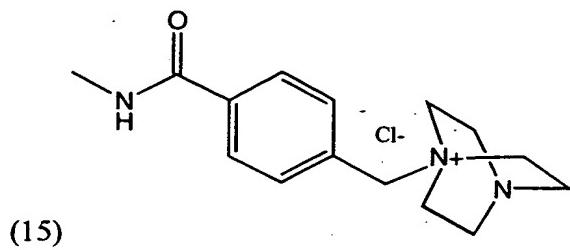
[546] 82. The compound of embodiment 1 wherein said compound of Formula I-1 comprises Formula I-17 represented by:

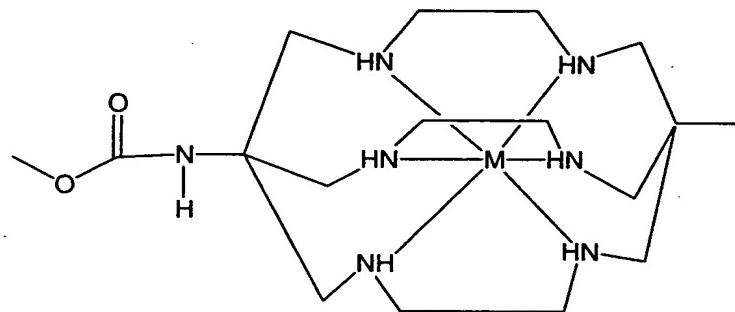
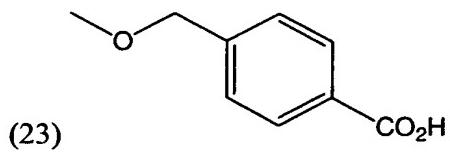
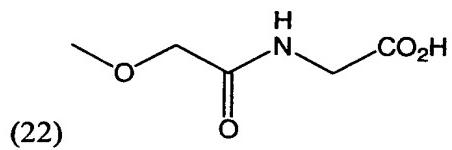
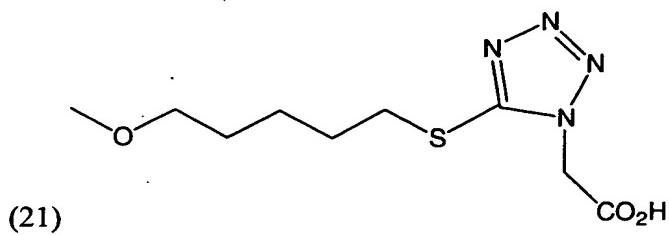


wherein R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{5A}, R^{5B}, R⁶, m and j are as previously defined and said R⁵ is selected from the group consisting of (1) - (69) and (70):

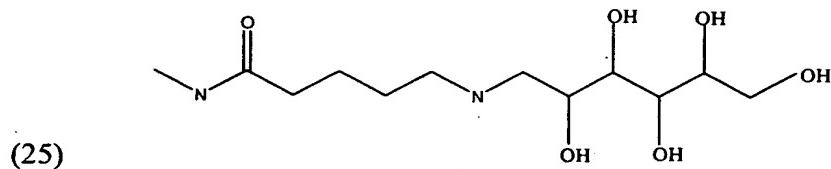


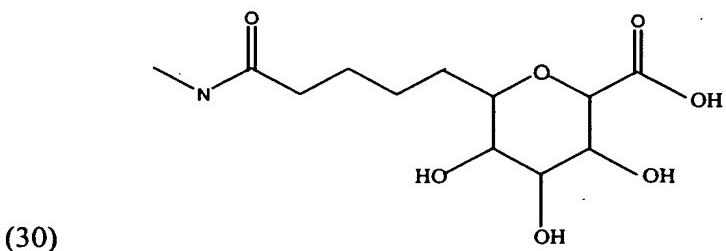
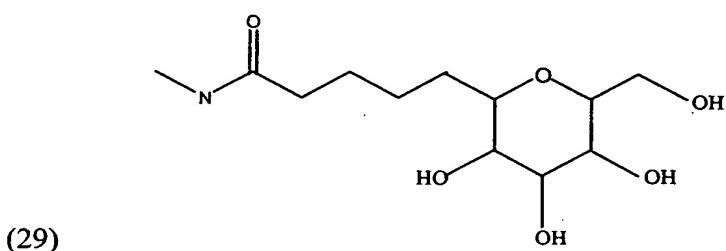
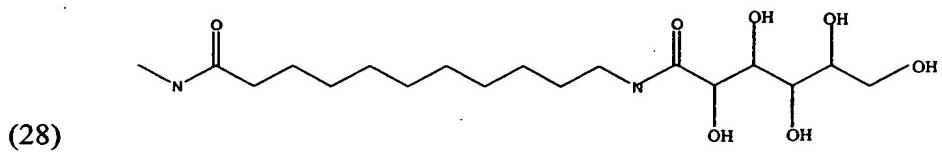
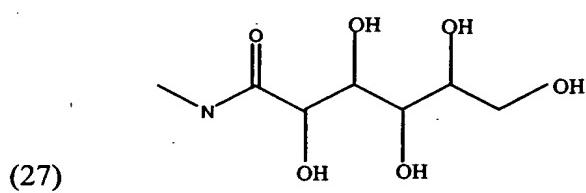
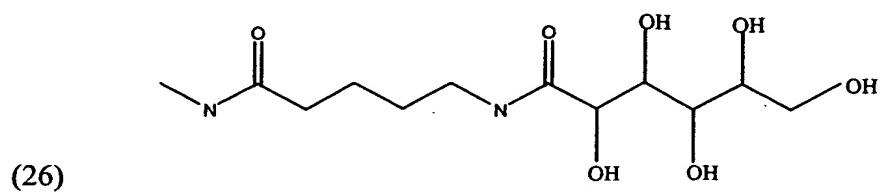


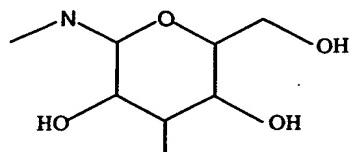




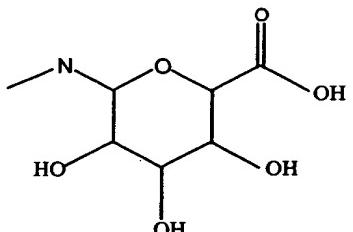
(24) $M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}



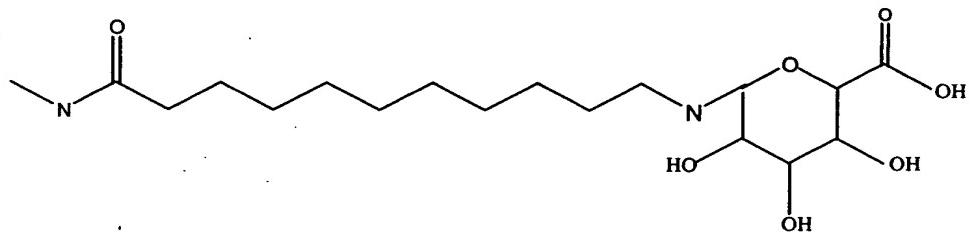




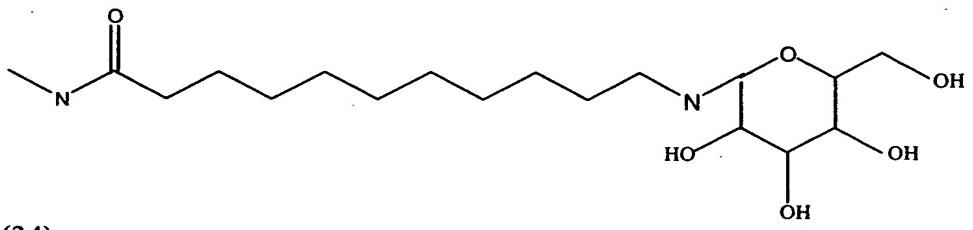
(31)



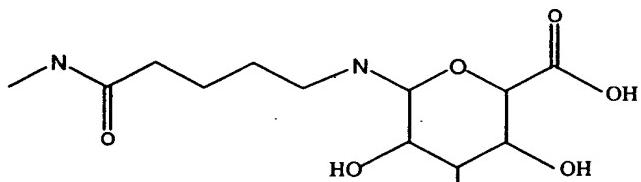
(32)



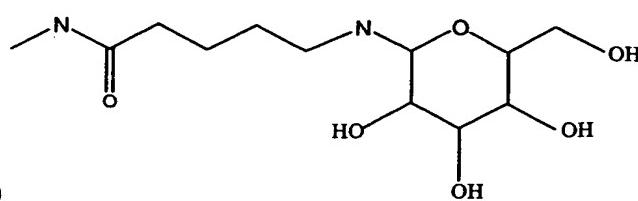
(33)



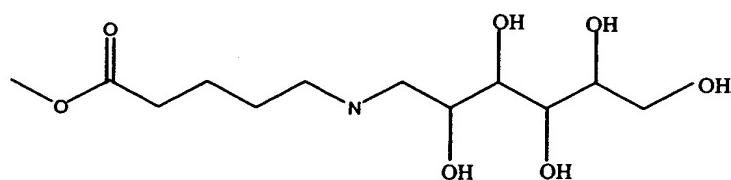
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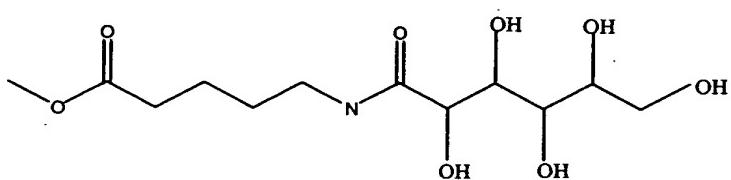
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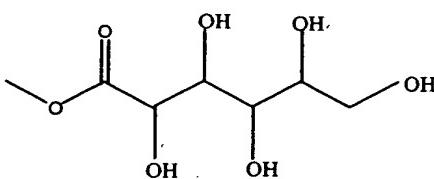
(36)



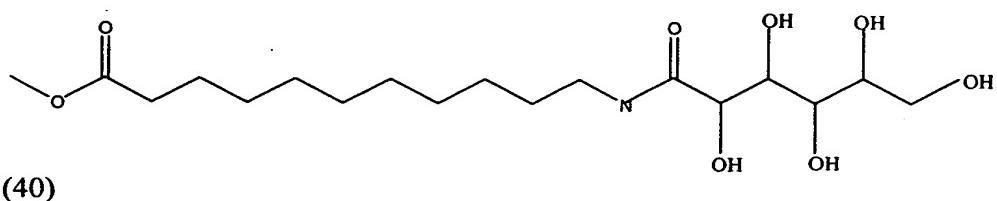
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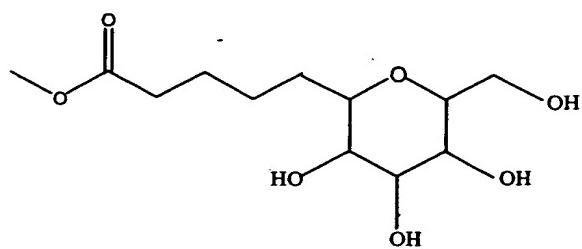
(38)



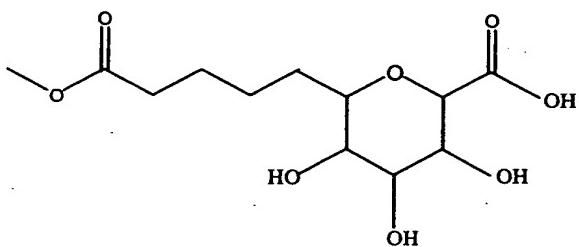
(39)



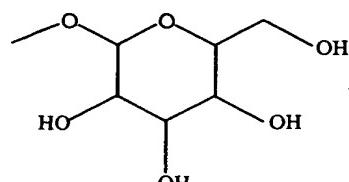
(40)



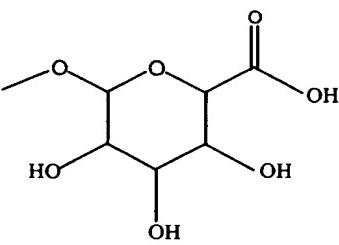
(41)



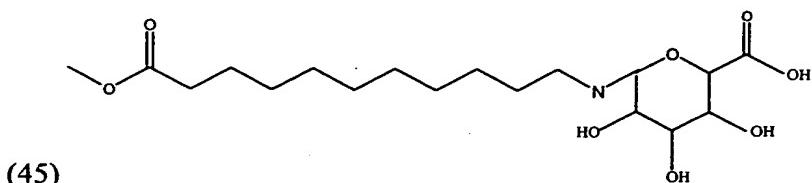
(42)



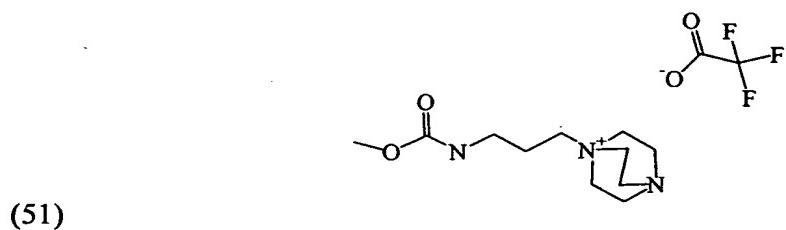
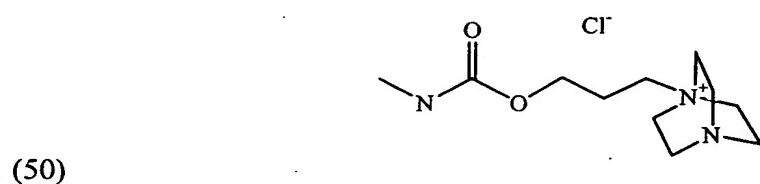
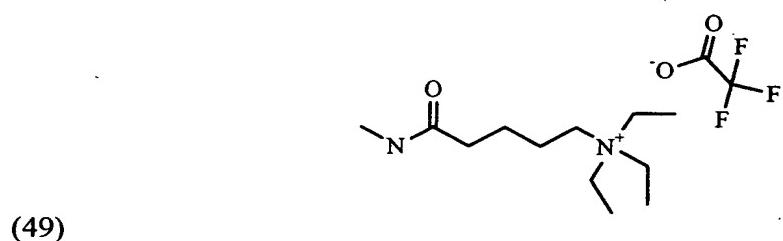
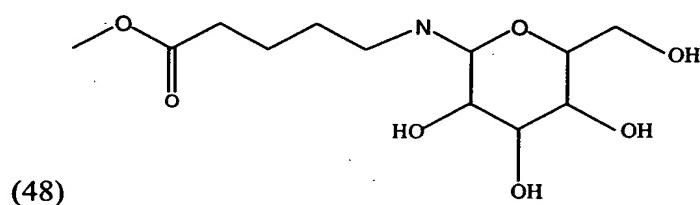
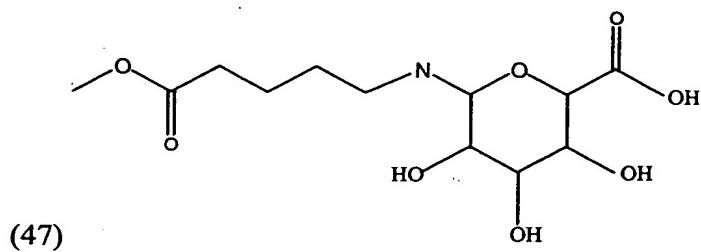
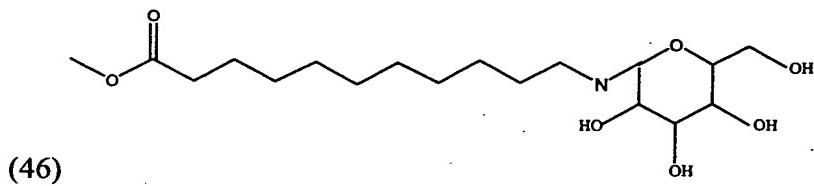
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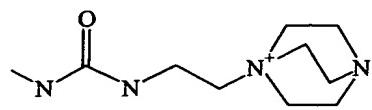


(44)



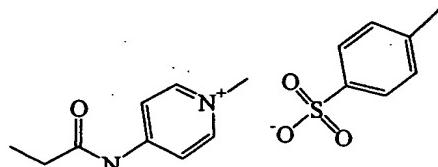
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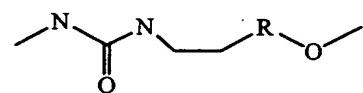


(52)

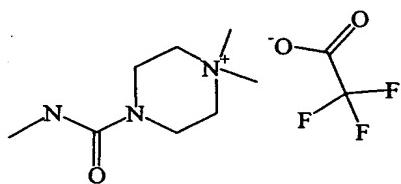
Cl⁻



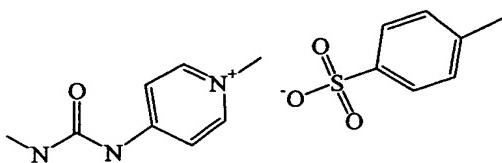
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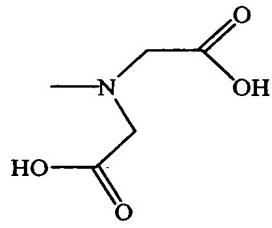
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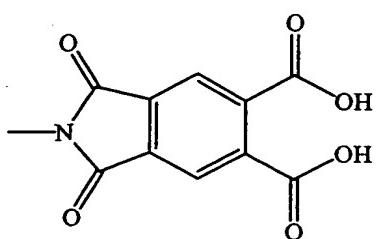
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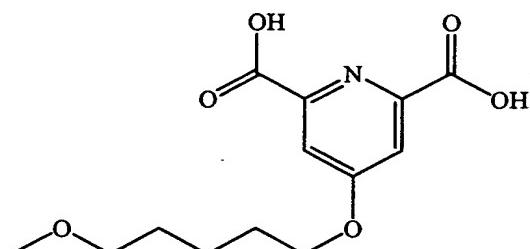
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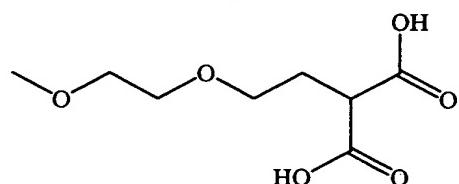
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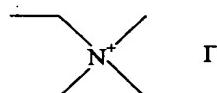
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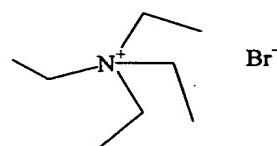
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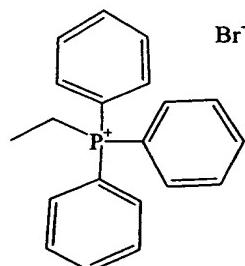
(60)



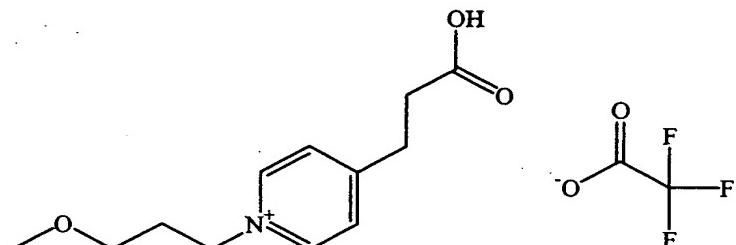
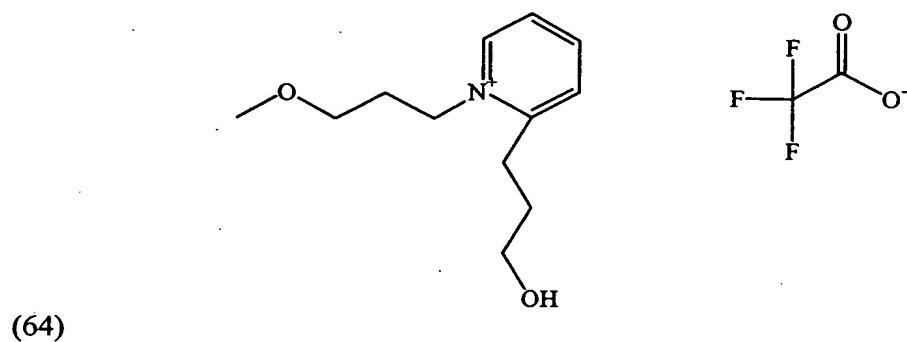
(61)



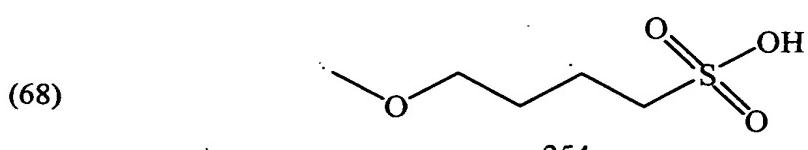
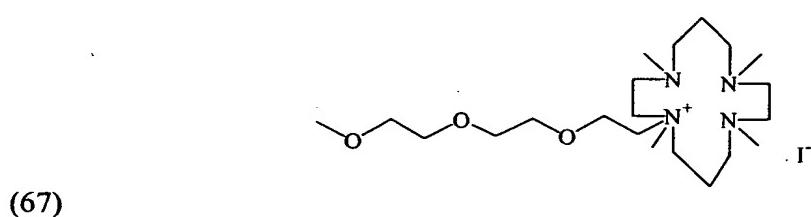
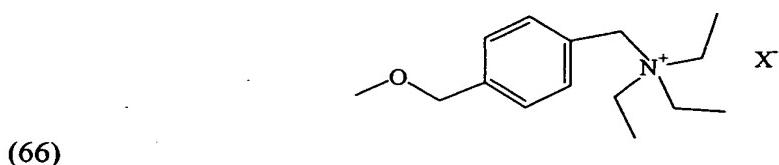
(62)

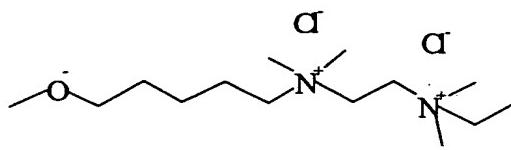


(63)

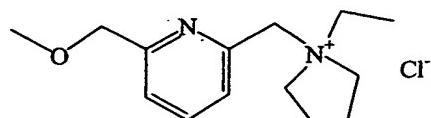


(65)





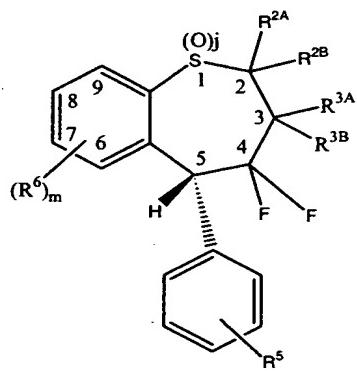
(69) and



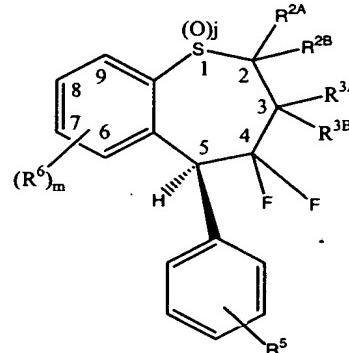
(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

[547] 83. The compound of embodiment 82 wherein said compound of Formula 17 comprises a member selected from the group consisting of Formulas I-21 and I-22 represented by:

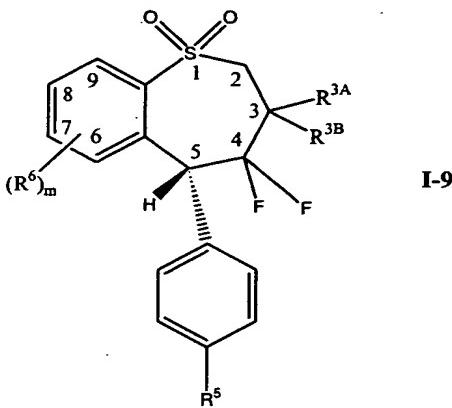


I-21.

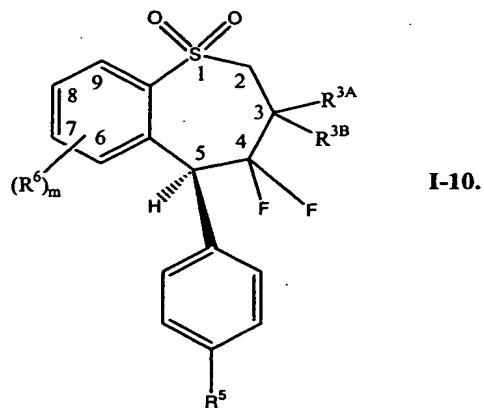


I-22.

[548] 84. The method of embodiment 83 wherein said compounds of Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:

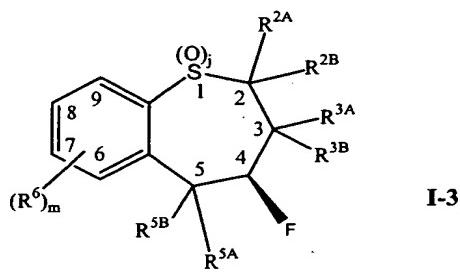


I-9

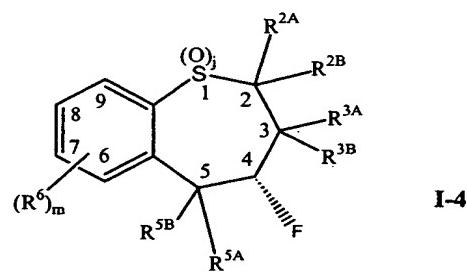


I-10.

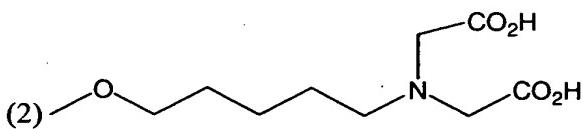
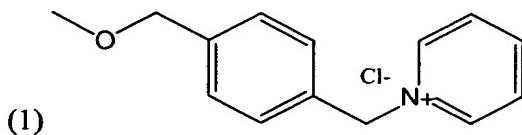
[549] 85. The compound of embodiment 1 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-3 and I-4 represented by:

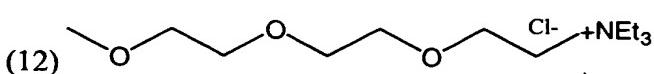
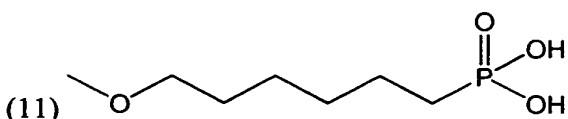
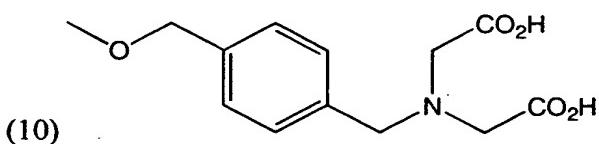
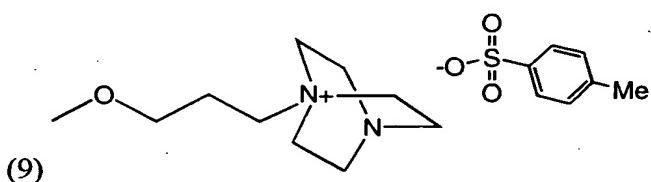
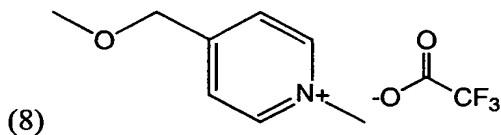
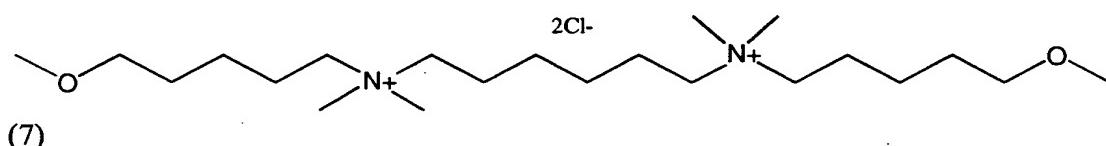
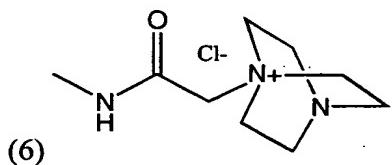
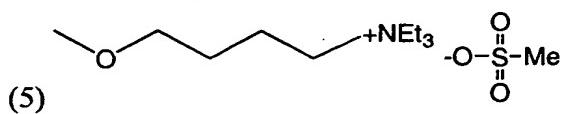
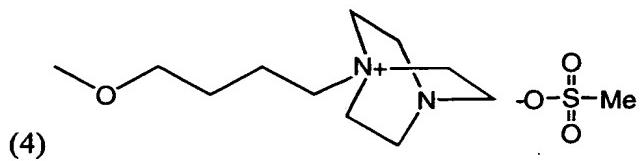
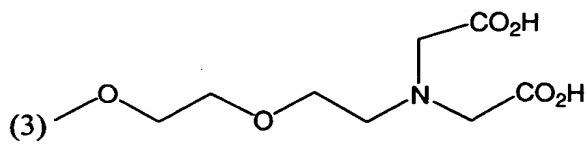


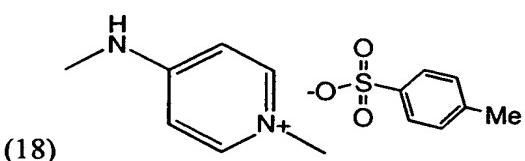
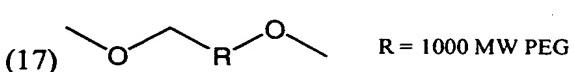
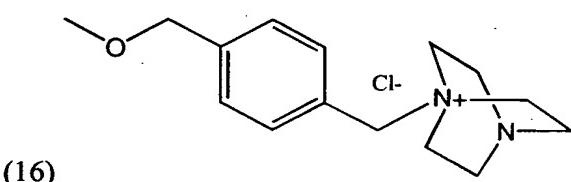
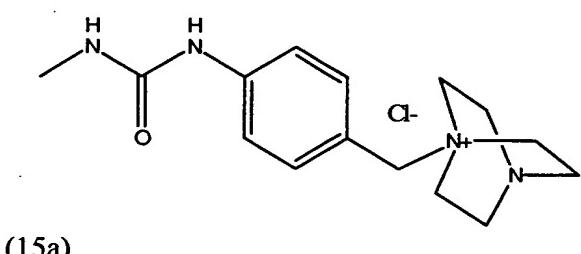
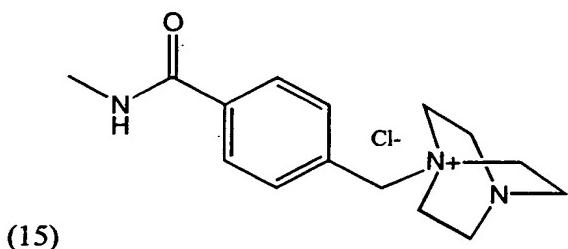
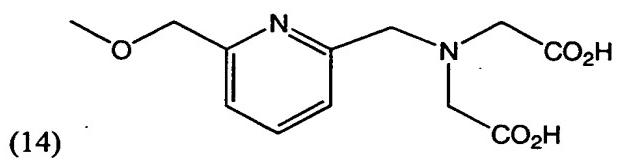
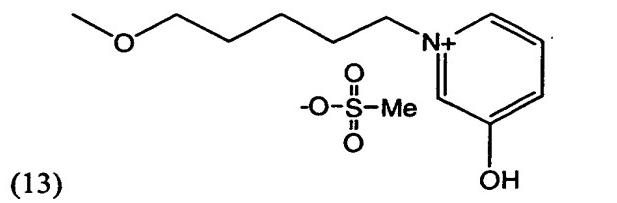
I-3

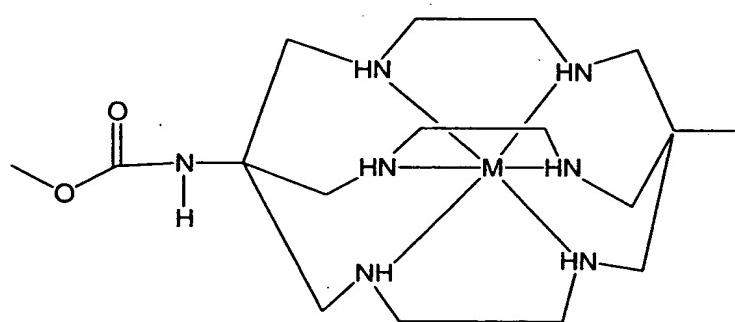
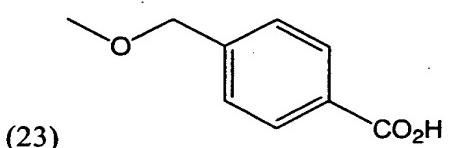
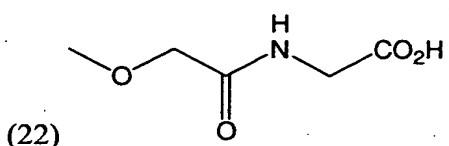
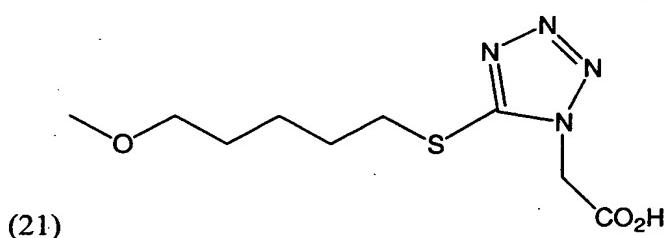
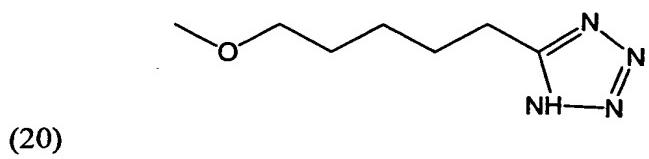
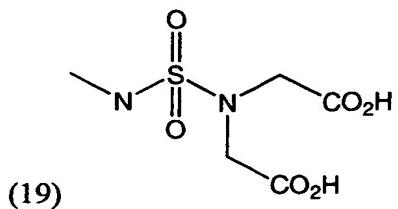


wherein R^{2A}, R^{2B}, R^{3A}, R^{3B}, R^{5A}, R^{5B}, R⁶, m and j are as previously defined and said R⁵ is selected from the group consisting of (1) – (69) and (70):

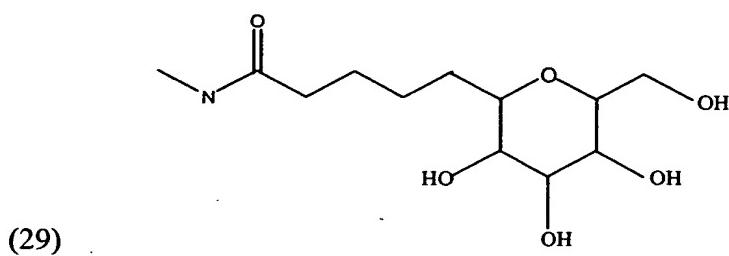
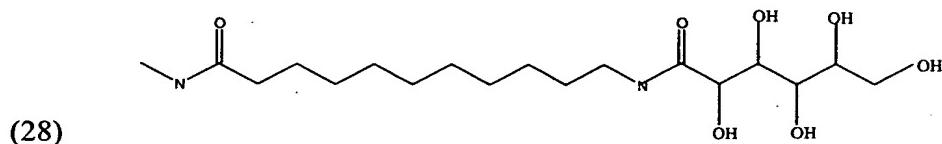
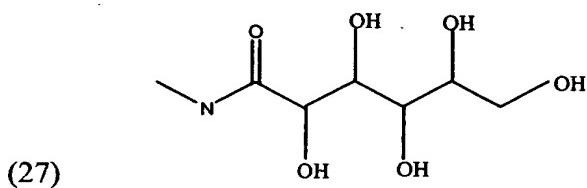
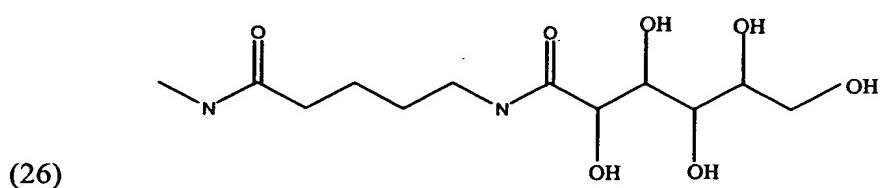
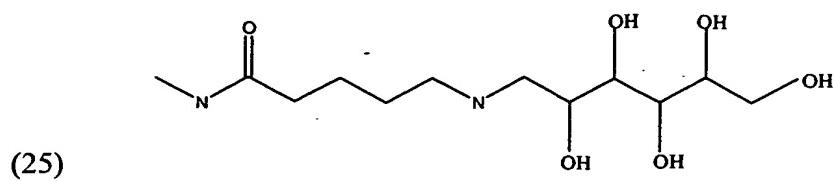


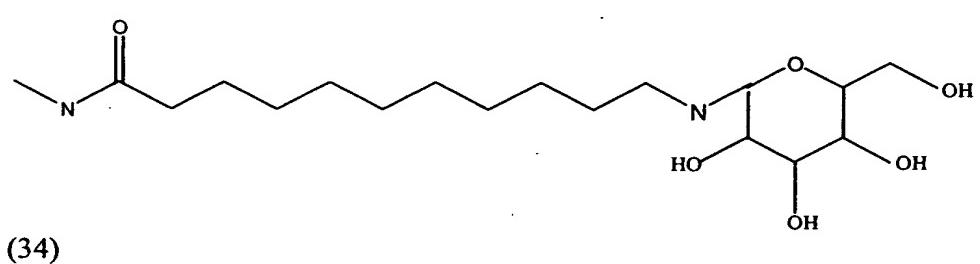
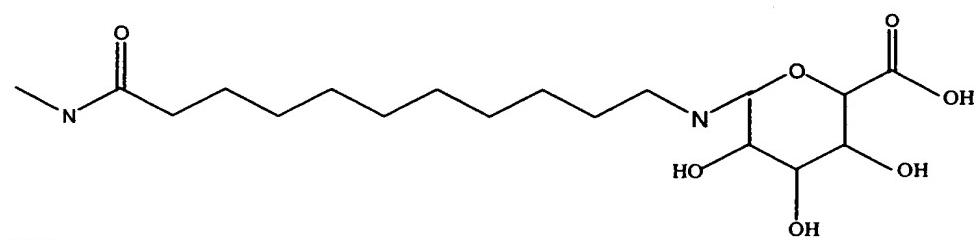
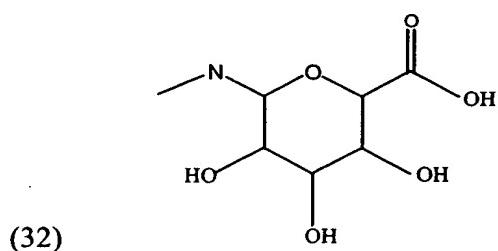
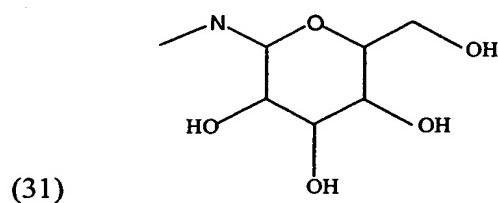
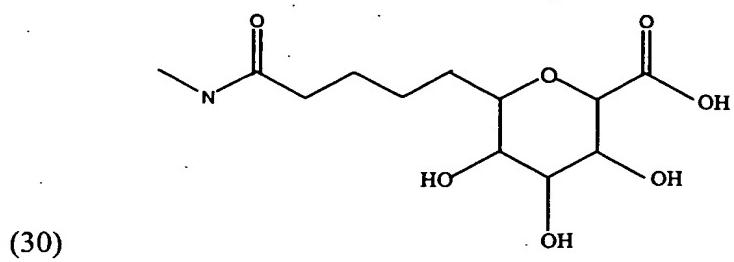


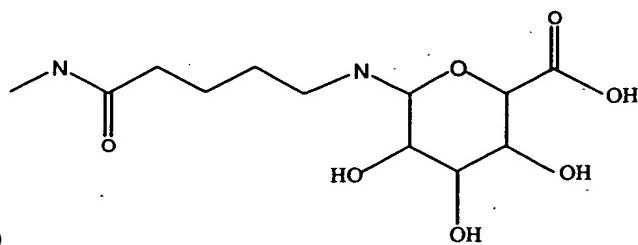




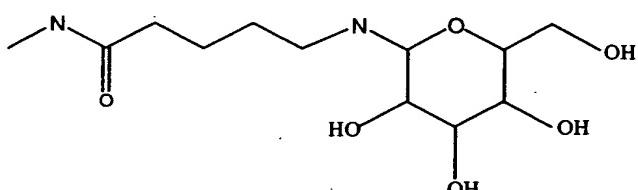
(24) $M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}



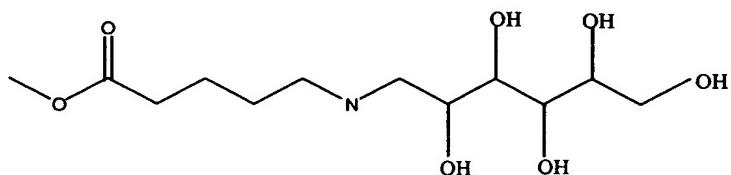




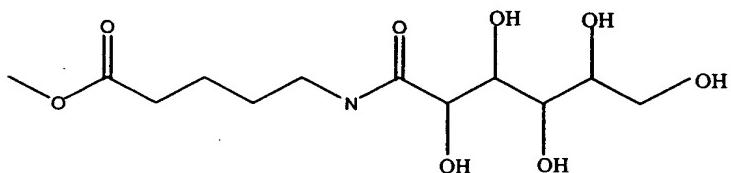
(35)



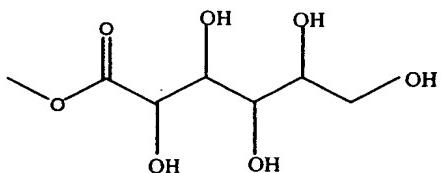
(36)



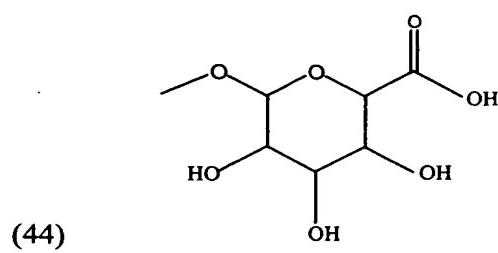
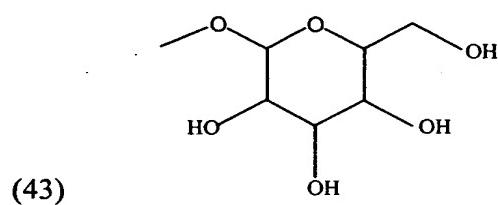
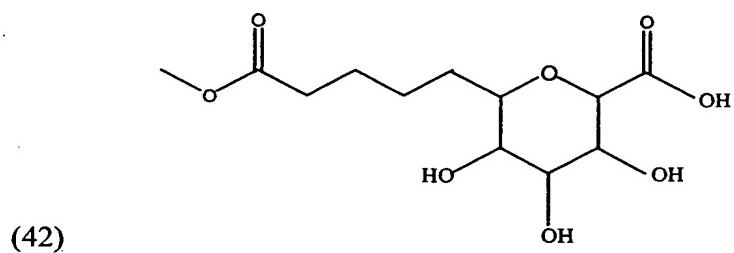
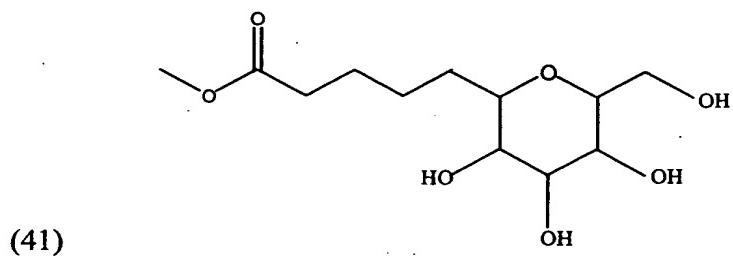
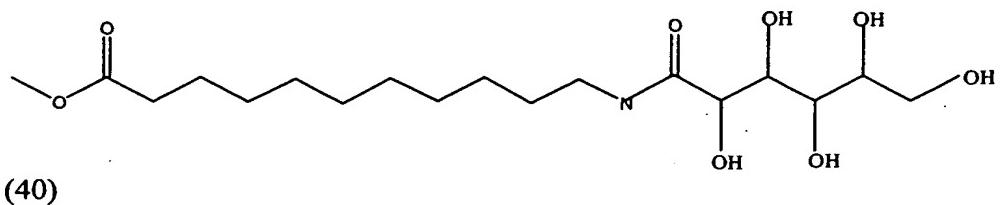
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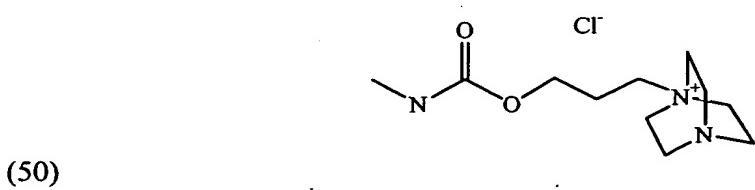
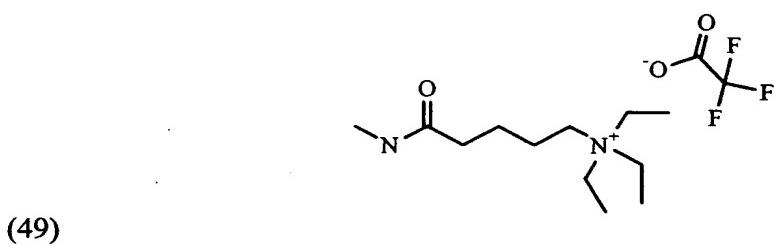
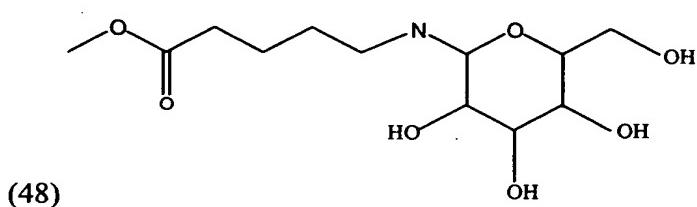
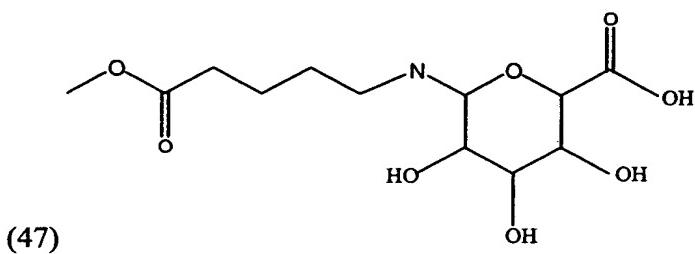
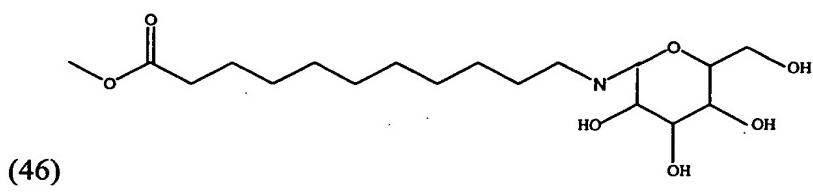
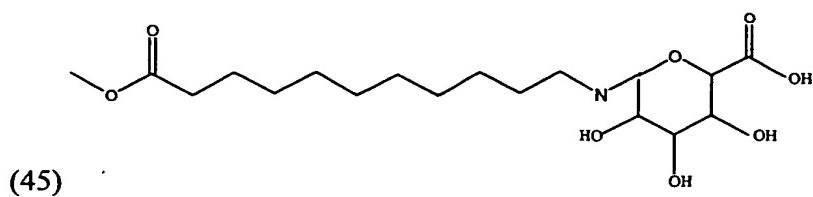


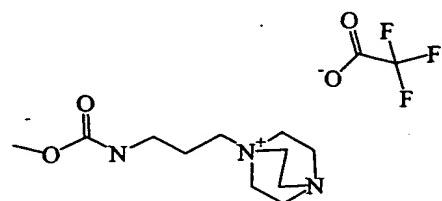
(38)



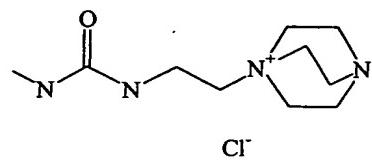
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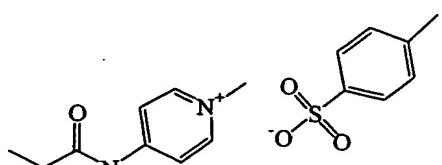




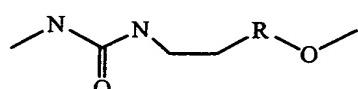
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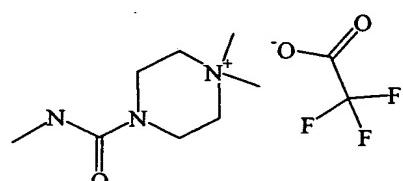
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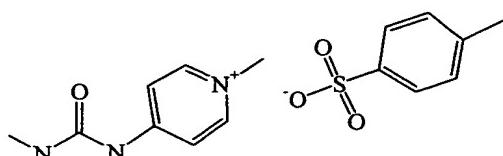
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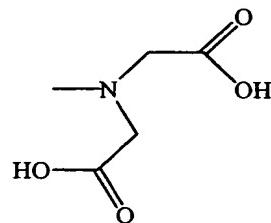
(54)



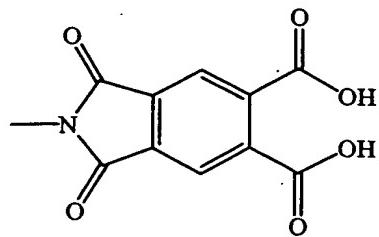
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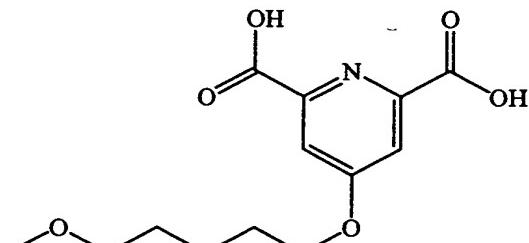
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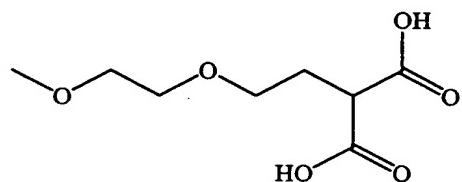
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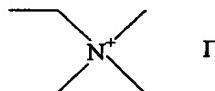
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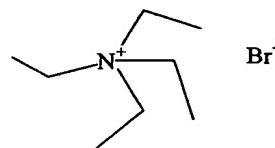
(59)



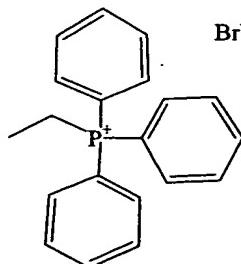
(60)



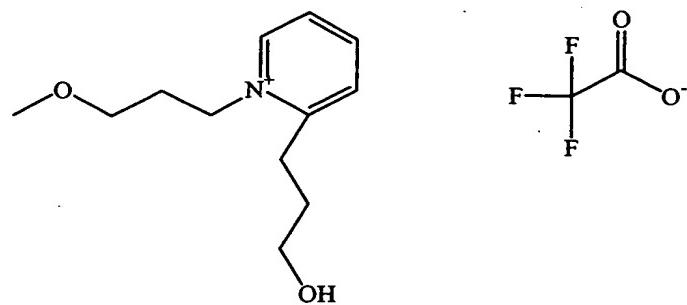
(61)



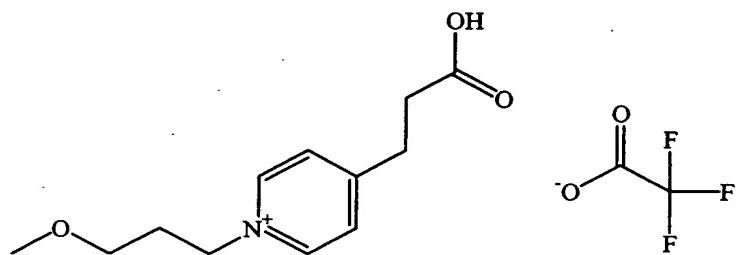
(62)



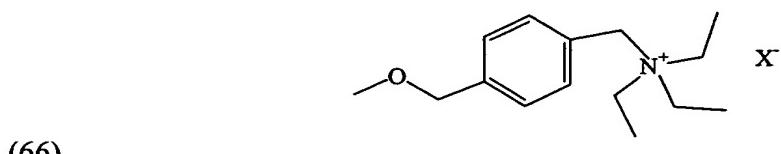
(63)



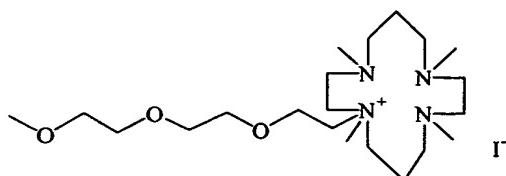
(64)



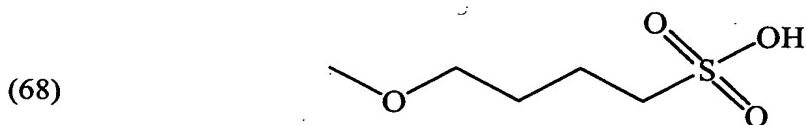
(65)



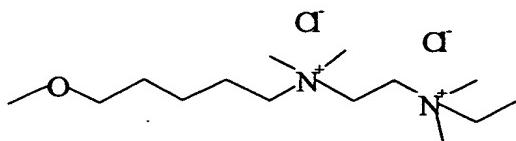
(66)



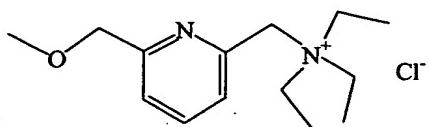
(67)



(68)



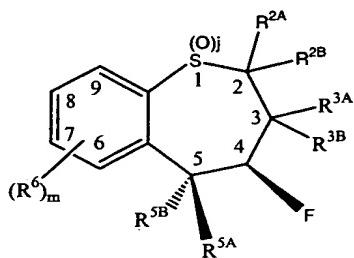
(69) and



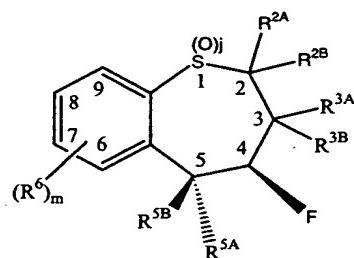
(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

[550] 86. The compound of embodiment 85 wherein said Formula I-3 comprises a member selected from the group consisting of Formulas I-5 and I-6 represented by:

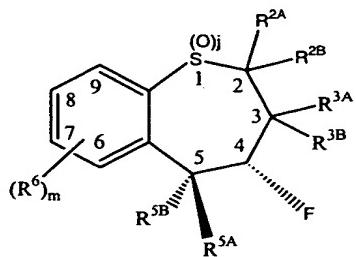


I-5

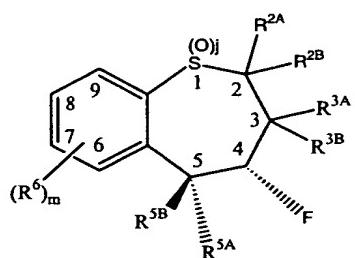


I-6.

[551] 87. The compound of embodiment 85 wherein said Formula I-4 comprises a member selected from the group consisting of Formulas I-7 and I-8 represented by:

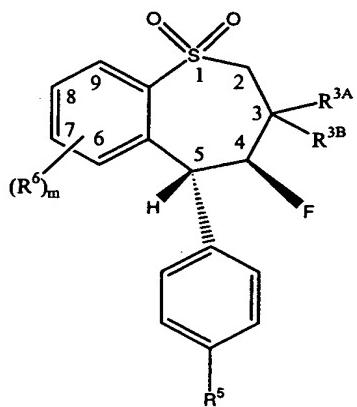


I-7

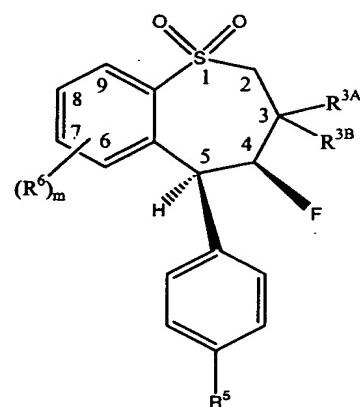


I-8.

[552] 88. The compound of embodiment 86 wherein said compounds of Formulas I-6 and I-5 comprise Formulas I-13 and I-14, respectively, represented by:

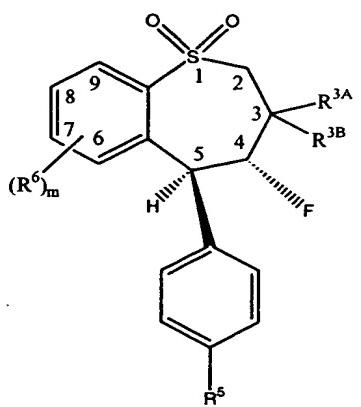


I-13

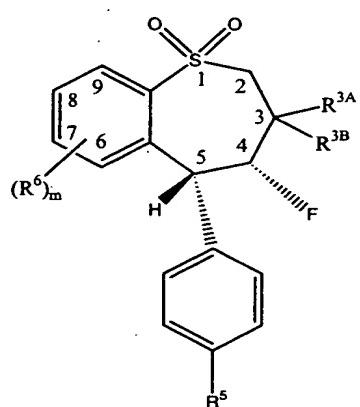


I-14.

[553] 89. The compound of embodiment 87 wherein said compounds of Formulas I-7 and I-8 comprise Formulas I-15 and I-16, respectively, represented by:

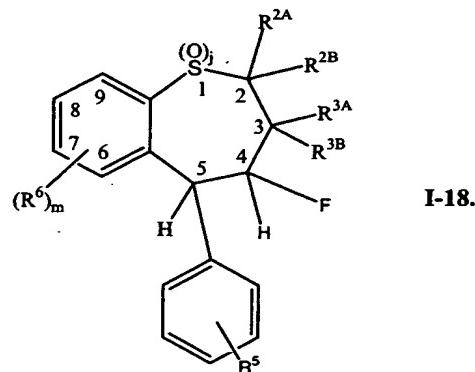


I-15

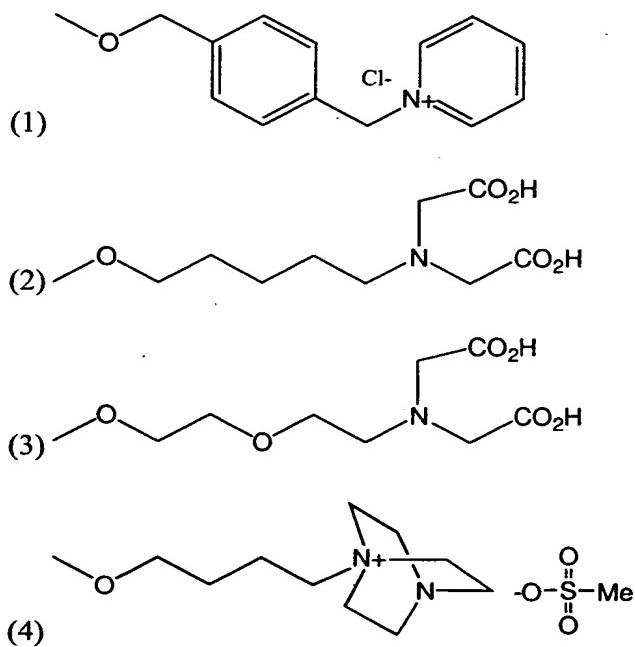


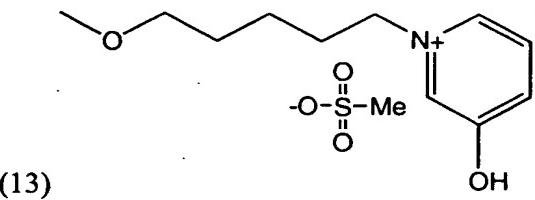
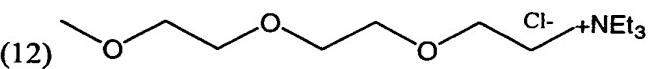
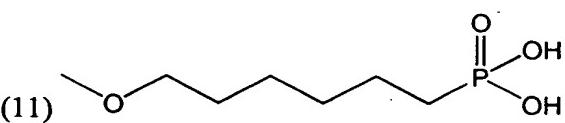
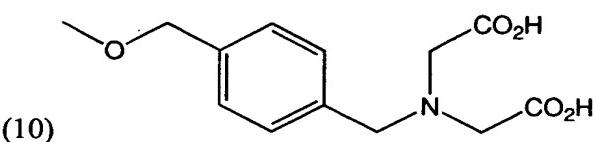
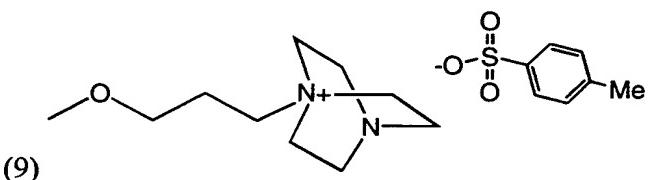
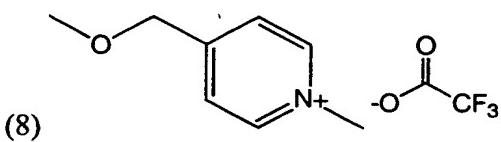
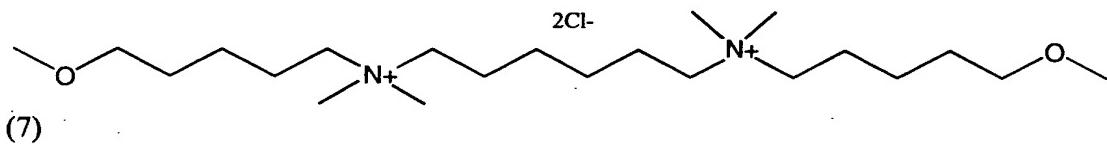
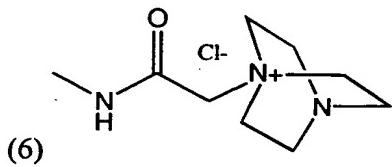
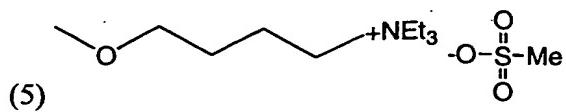
I-16.

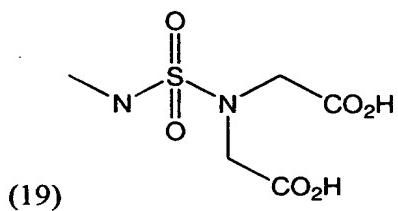
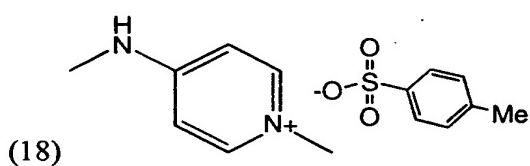
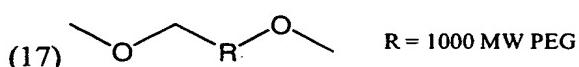
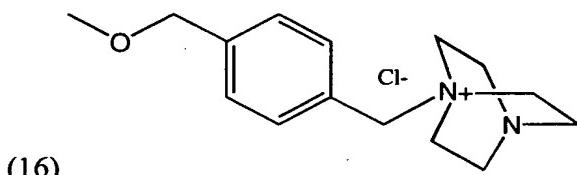
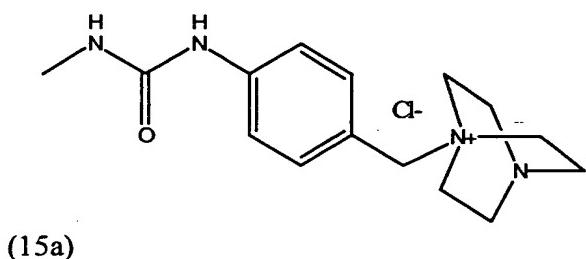
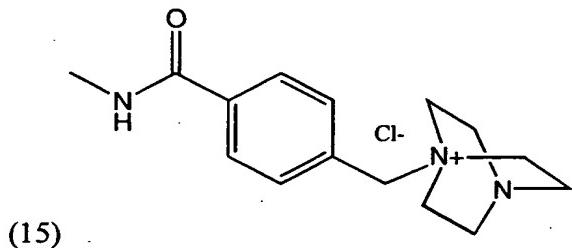
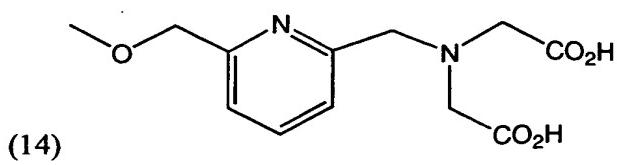
[554] 90. The compound of embodiment 1 wherein said compound of Formula I-2 comprises a compound of Formula I-18 represented by:

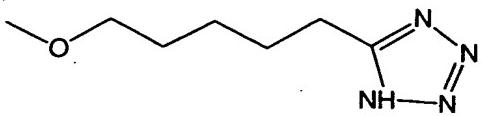


wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined and said R^5 is selected from the group consisting of (1) - (69) and (70):

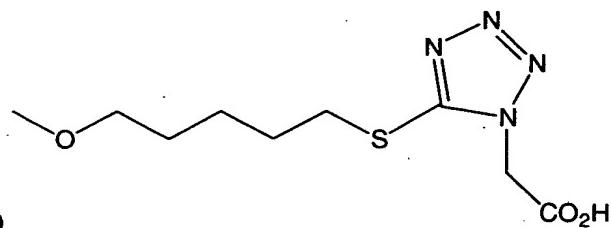




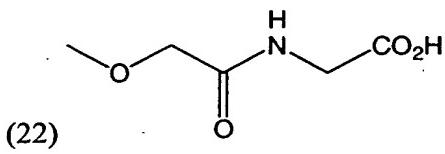




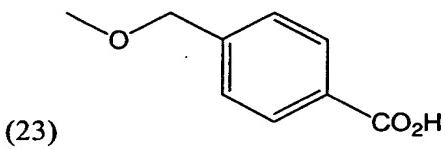
(20)



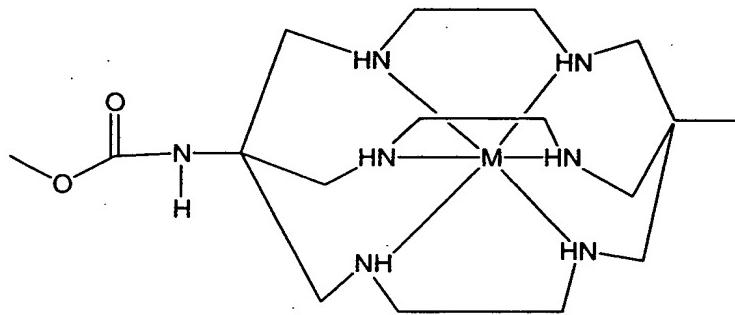
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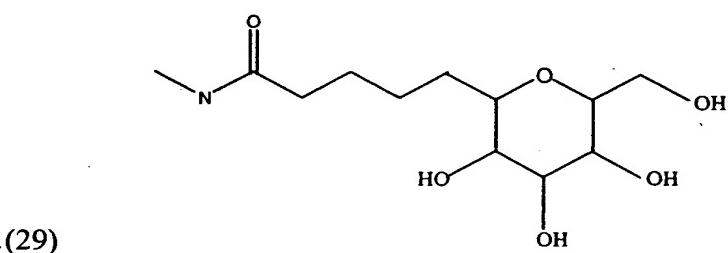
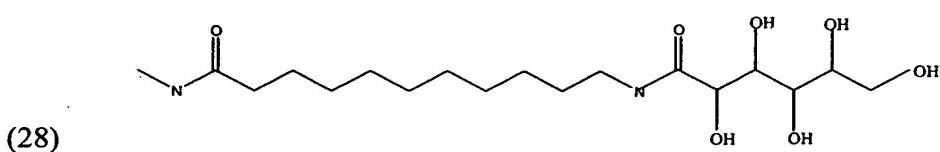
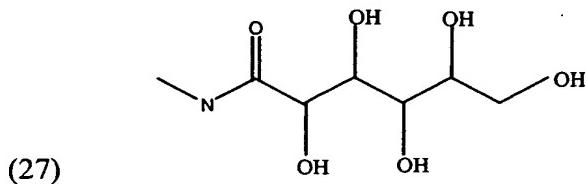
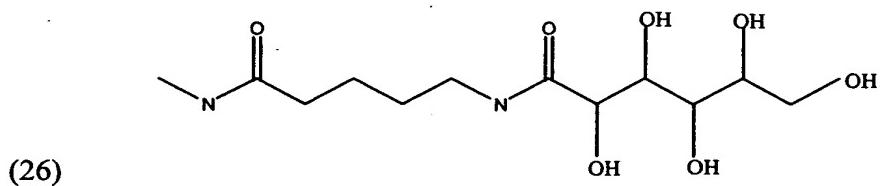
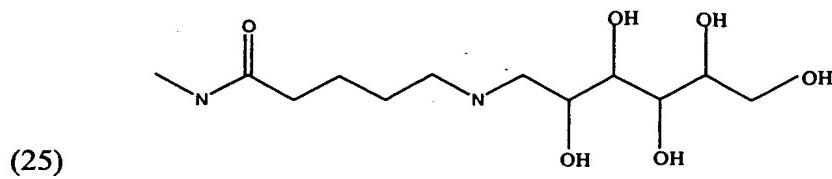
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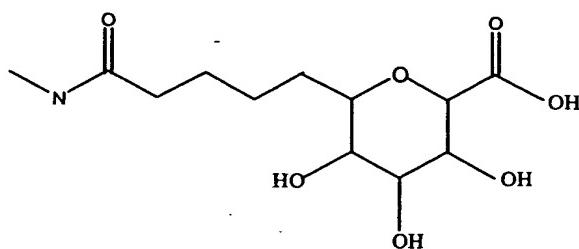


(23)

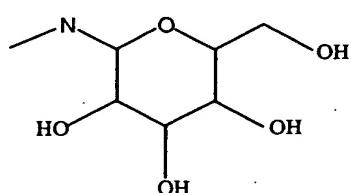


(24) $\text{M} = \text{Co}^{\text{II}}, \text{III}, \text{Mn}^{\text{II}}, \text{III}, \text{Fe}^{\text{II}}, \text{III}, \text{Ni}^{\text{II}}, \text{III},$
 $\text{Cr}^{\text{III}}, \text{Cu}^{\text{II}}, \text{Zn}^{\text{II}}, \text{Cd}^{\text{II}}, \text{Ga}^{\text{III}}, \text{In}^{\text{III}}, \text{V}^{\text{IV}},$
 $\text{Ru}^{\text{II}}, \text{Pr}^{\text{IV}}, \text{Rh}^{\text{III}} \text{ or Ir}^{\text{III}}$

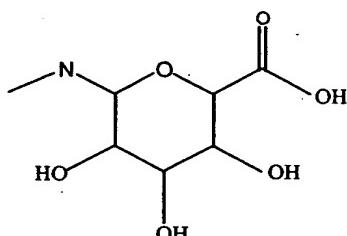




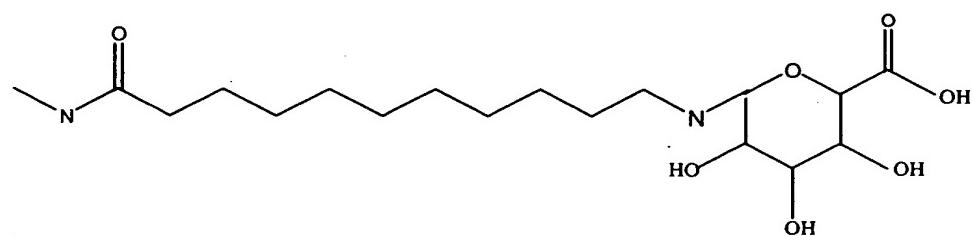
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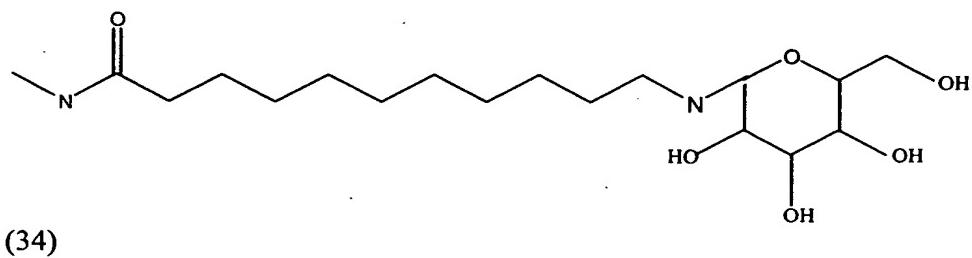
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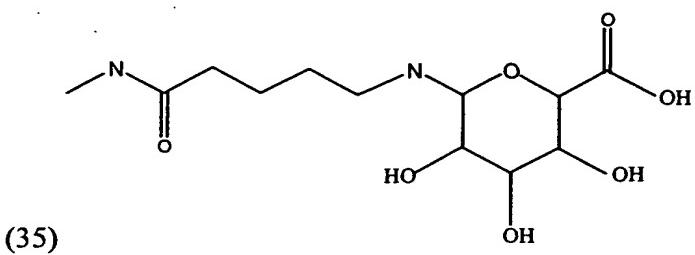
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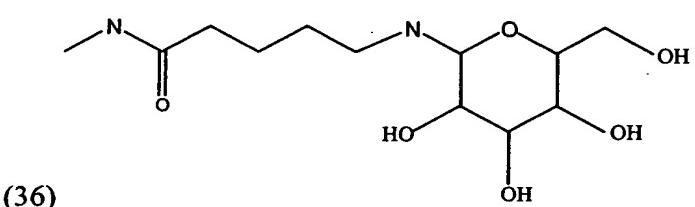
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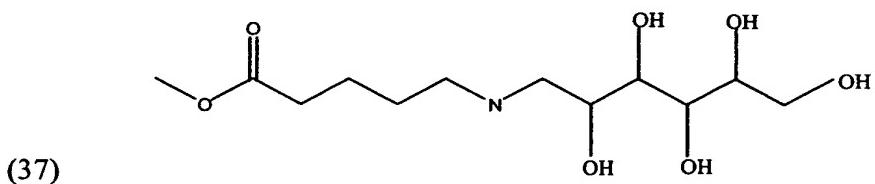
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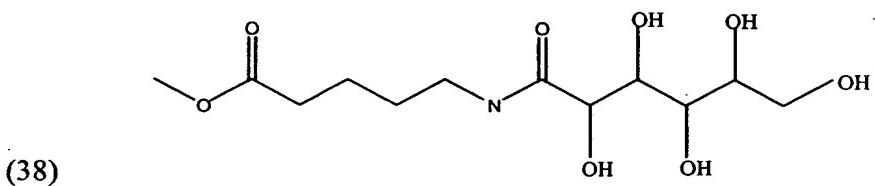
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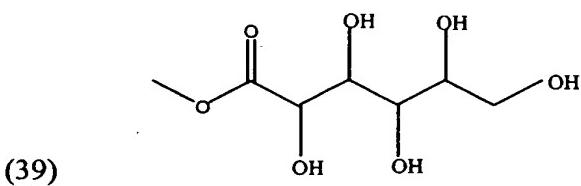
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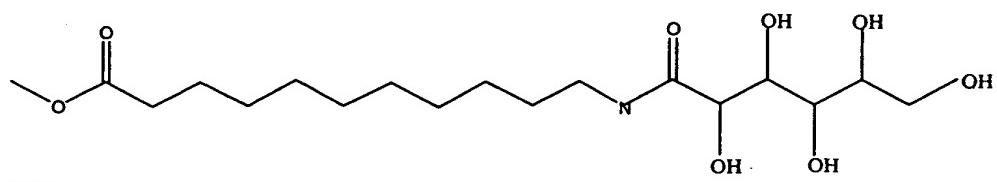
(37)



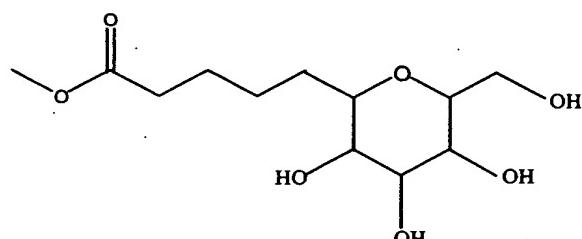
(38)



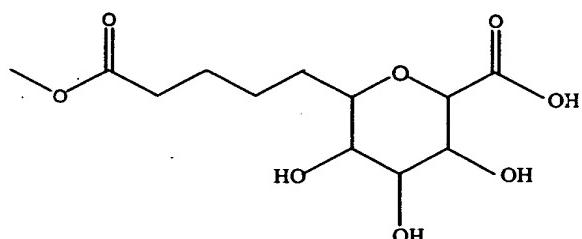
(39)



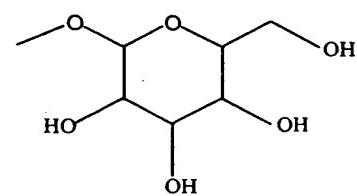
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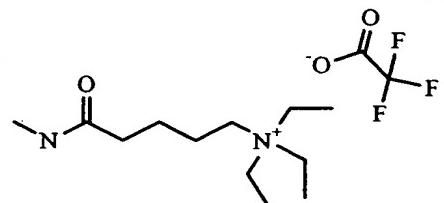
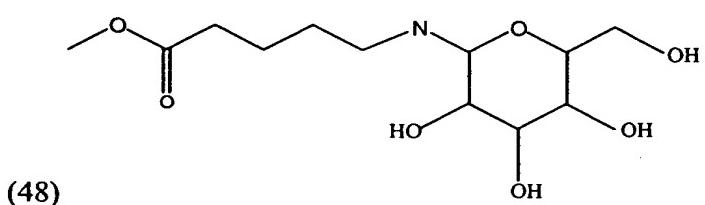
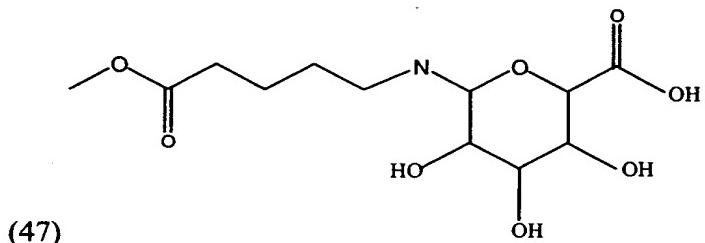
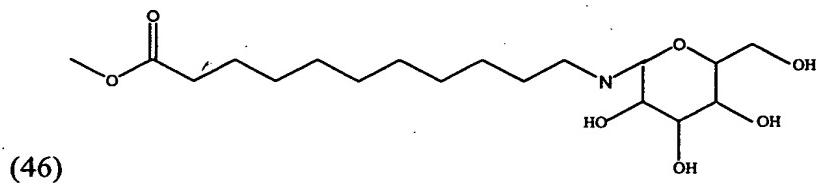
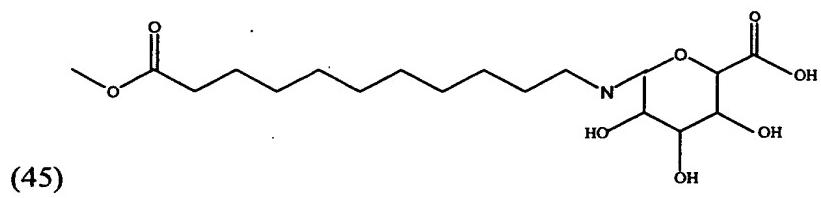
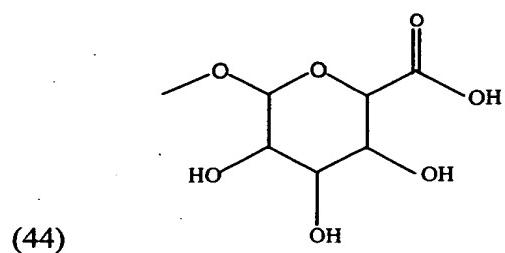
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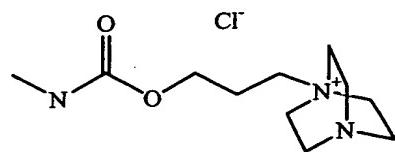
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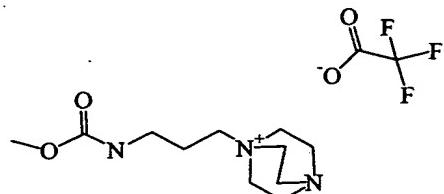
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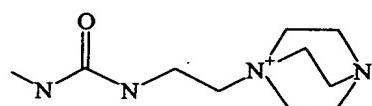
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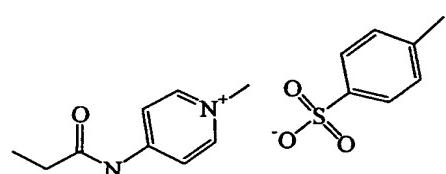
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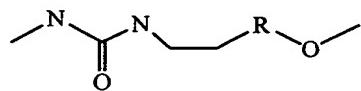
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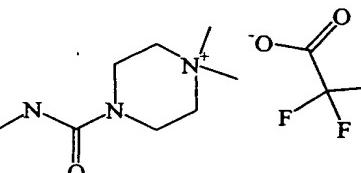
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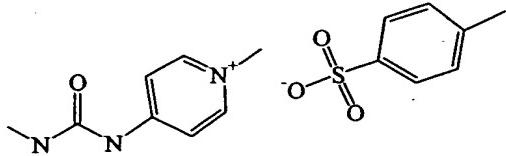
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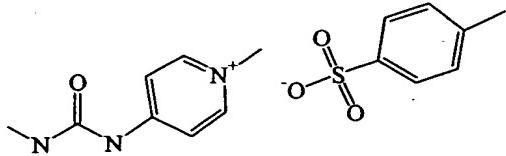
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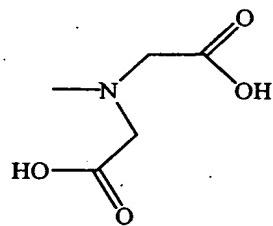


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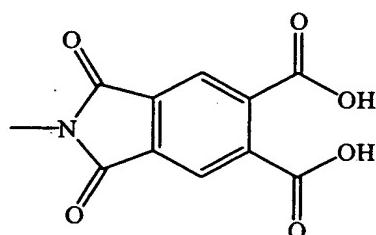


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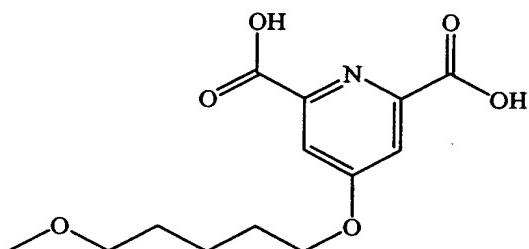




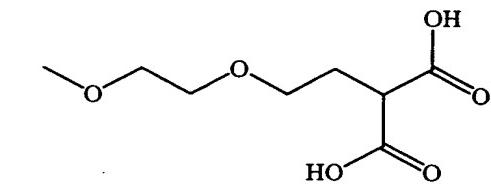
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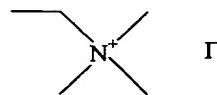
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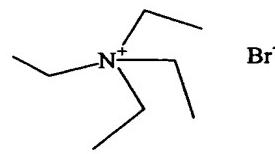
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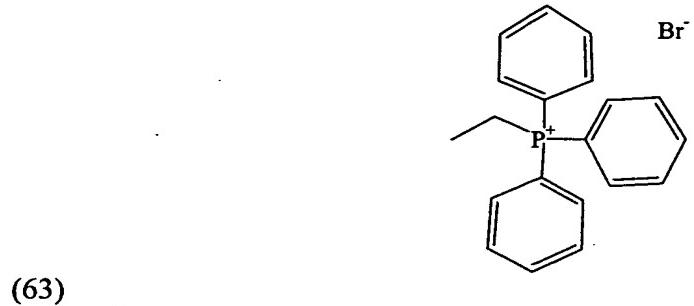
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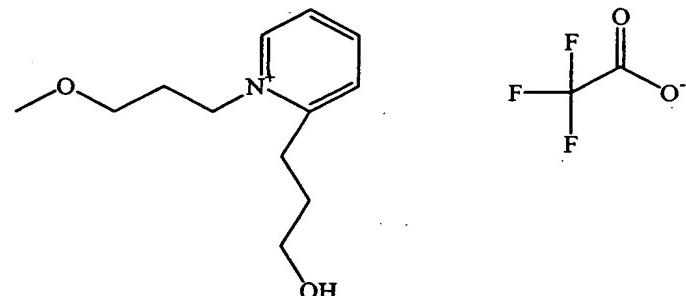
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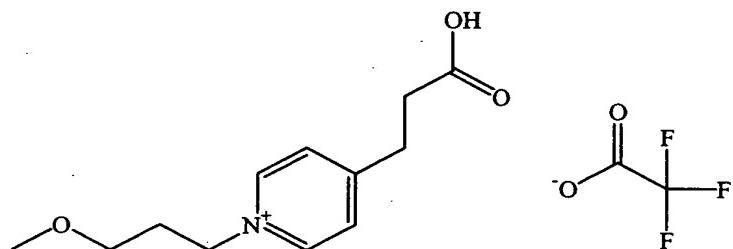
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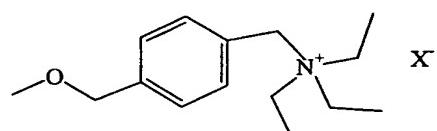
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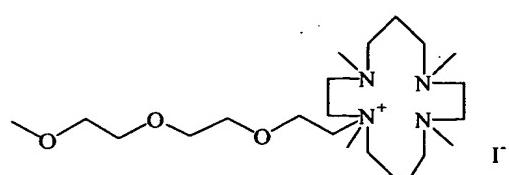
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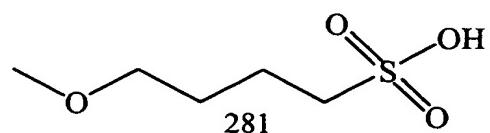
(65)



(66)

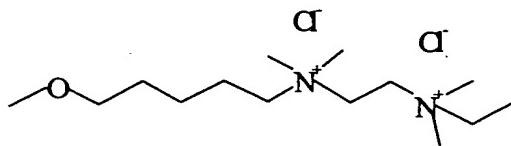


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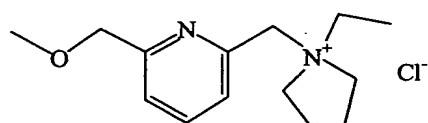


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(68)



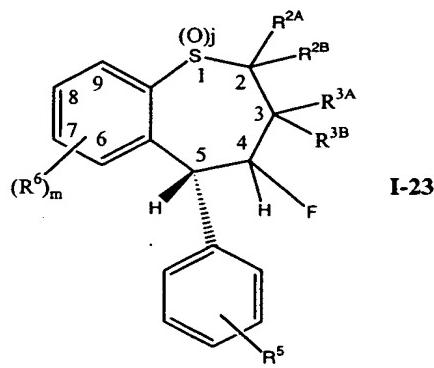
(69) and



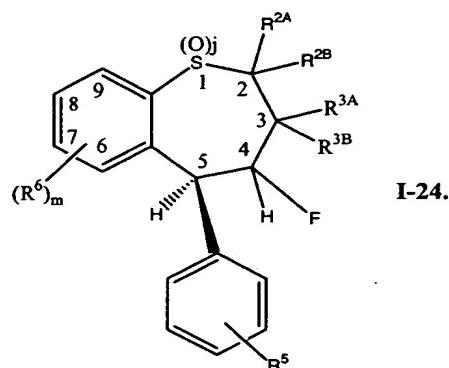
(70)

provided that when said R^5 is (7), (17) or (24), then said R^{5A} is a left end of said R^5 and said R^{5B} is a right end of said R^5 or vice versa.

[555] 91. The compound of embodiment 90 wherein said compound of Formula I-18 comprises a member selected from the group consisting of I-23 and I-24 represented by:

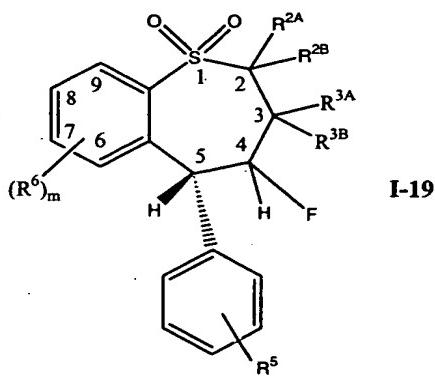


I-23

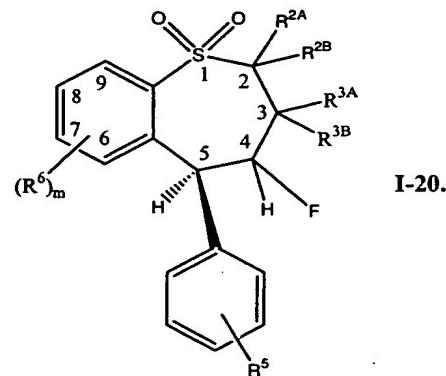


I-24.

[556] 92. The compound of embodiment 91 wherein said compounds of Formulas I-23 and I-24 comprise compounds of Formulas I-19 and I-20, respectively, represented by:

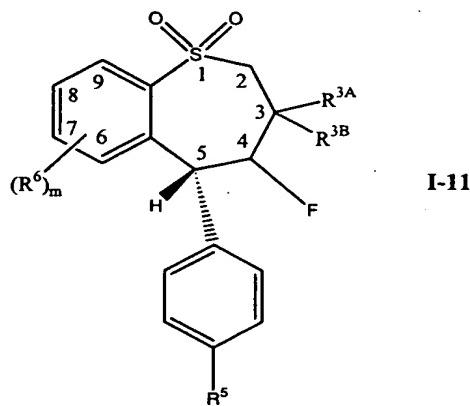


I-19

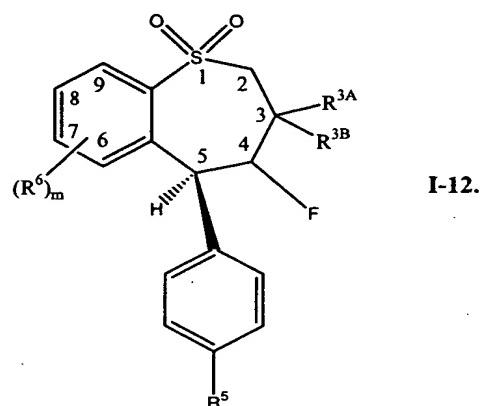


I-20.

[557] 93. The compound of embodiment 1 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-11 and I-12 represented by:



I-11



I-12.

[558] 94. The method of embodiment 39 wherein said hyperlipidemic condition is hypercholesterolemia.

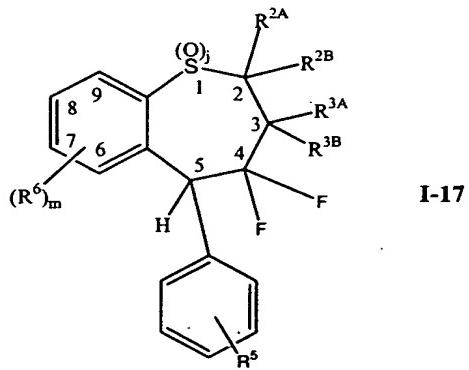
- [559] 95. The method of embodiment 94 wherein said therapeutically effective amount is a daily dose from about 0.001 mg to about 10,000 mg.
- [560] 96. The method of embodiment 95 wherein said daily dose is from about 0.005 mg to about 1,000 mg.
- [561] 97. The method of embodiment 96 wherein said daily dose is from about 0.008 to about 100 mg.
- [562] 98. The method of embodiment 97 wherein said daily dose is from about 0.05 mg to about 50 mg.
- [563] 99. The method of embodiments 95- 98 wherein said daily dose is administered as a single dose or in multiple divided doses.
- [564] 100. The method of embodiment 40 wherein said therapeutically effective amount is a daily dose from about 0.001 mg to about 10,000 mg.
- [565] 101. The method of embodiment 100 wherein said daily dose is from about 0.005 mg to about 1,000 mg.
- [566] 102. The method of embodiment 101 wherein said daily dose is from about 0.008 to about 100 mg.

- [567] 103. The method of embodiment 102 wherein said daily dose is from about 0.05 mg to about 50 mg.
- [568] 104. The method of embodiments 100 – 103 wherein said daily dose is administered as a single dose or in multiple divided doses.
- [569] 105. The method of embodiment 95 wherein said daily dose is administered orally.
- [570] 106. The method of embodiment 95 wherein said daily dose is administered parenterally.
- [571] 107. The method of embodiment 95 wherein said daily dose is administered rectally.
- [572] 108. The method of embodiment 107 wherein said daily dose is administered as a rectal dosage form comprising a suppository.
- [573] 109. The method of embodiment 94 wherein said therapeutically effective amount is administered as a slow release dosage form.
- [574] 110. The method of embodiment 109 wherein said slow release dosage form comprises an implant.

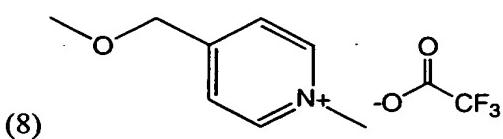
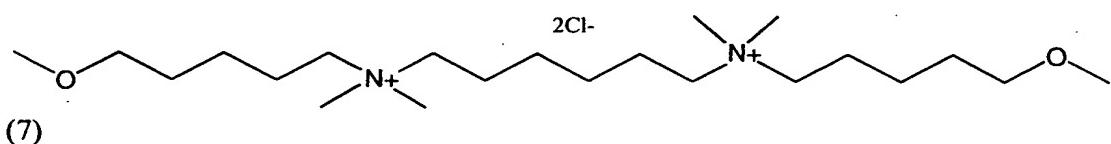
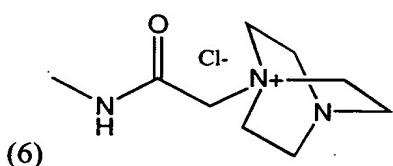
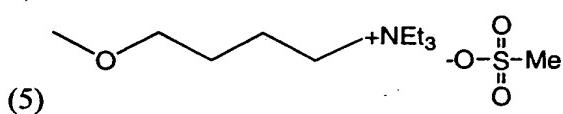
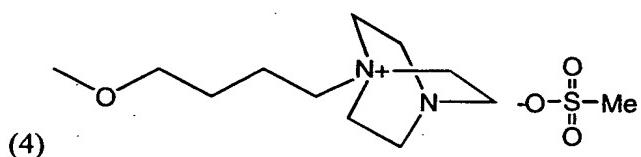
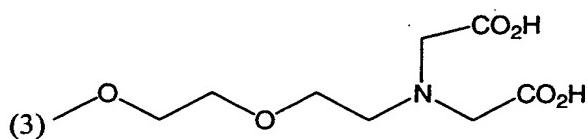
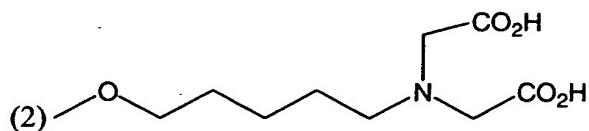
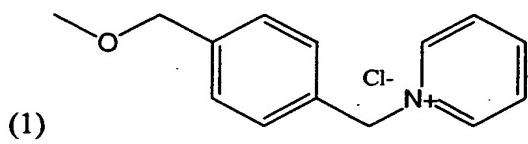
- [575] 111. The method of embodiment 105 wherein said daily dose is administered in the form of an oral dosage form selected from the group consisting of a tablet, a capsule, a powder, a solution, a suspension, an emulsion, and a syrup.
- [576] 112. The method of embodiment 111 wherein said solution comprises a syrup.
- [577] 113. The method of embodiment 111 wherein said oral dosage form comprises a sublingual tablet, an effervescent tablet, or a slow release tablet.
- [578] 114. The method of embodiment 106 wherein said parenteral dosage form is selected from the group consisting of an intramuscular injection, an intravenous injection, and a subcutaneous injection.
- [579] 115. The method of embodiment 95 wherein said daily dose is administered topically.
- [580] 116. The method of embodiment 100 wherein said daily dose is administered parenterally.
- [581] 117. The method of embodiment 100 wherein said daily dose is administered rectally or vaginally.

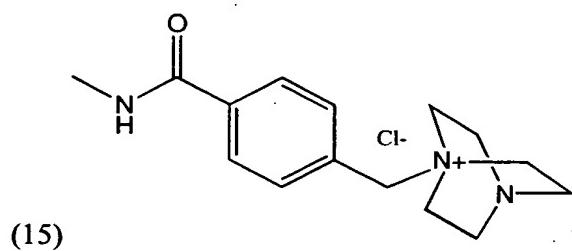
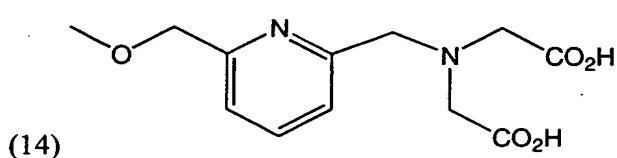
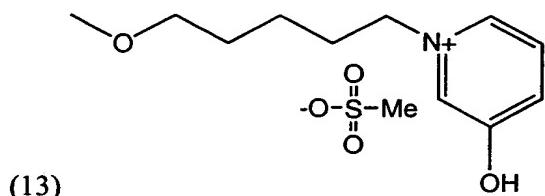
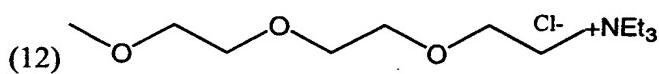
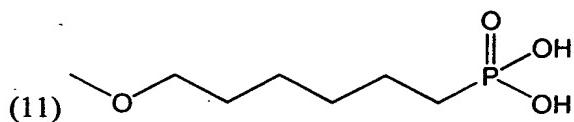
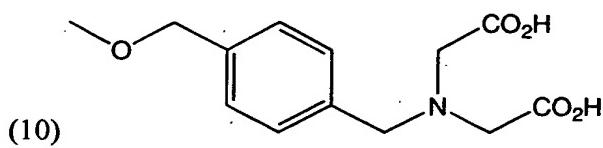
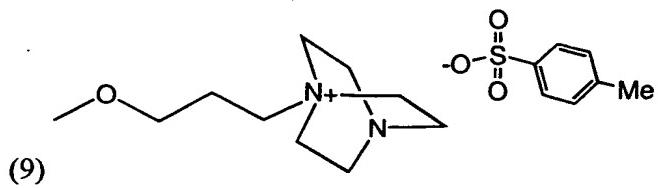
- [582] 118. The method of embodiment 117 wherein said daily dose is administered as a rectal dosage form or a vaginal dosage form comprising a suppository.
- [583] 119. The method of embodiment 100 wherein said daily dose is administered as a slow release dosage form.
- [584] 120. The method of embodiment 119 wherein said slow release dosage form comprises an implant.
- [585] 121. The method of embodiment 100 wherein said daily dose is administered in the form of an oral dosage form selected from the group consisting of a tablet, a capsule, a powder, a solution, a suspension, and an emulsion.
- [586] 122. The method of embodiment 121 wherein said solution comprises a syrup.
- [587] 123. The method of embodiment 121 wherein said tablet comprises a sublingual tablet, an effervescent tablet, or a slow release tablet.
- [588] 124. The method of embodiment 116 wherein said parenteral dosage form is selected from the group consisting of an intramuscular injection, an intravenous injection, and a subcutaneous injection.

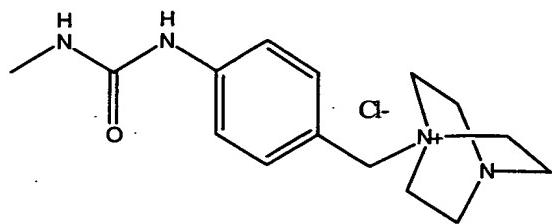
- [589] 125. The method of embodiment 100 wherein said daily dose is administered topically.
- [590] 126. The method of embodiment 125 wherein said daily dose is administered in the form of a topical dosage form selected from the group consisting of a lotion, a cream, a suspension, an emulsion, a paste, and a solution.
- [591] 127. The method of embodiment 115 wherein said daily dose is administered in the form of a topical dosage form selected from the group consisting of a lotion, a cream, a suspension, an emulsion, a paste, and a solution.
- [592] 128. A pharmaceutical composition comprising a compound of Formula I-1 or I-2 of embodiment 1 and a pharmaceutically acceptable carrier.
- [593] 129. The pharmaceutical composition of embodiment 128 wherein said compound of Formula I-1 comprises Formula I-17 represented by:



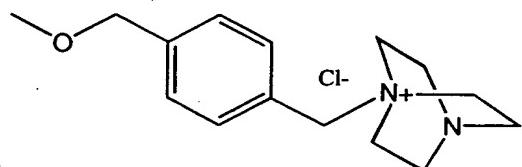
wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined and said R^5 is selected from the group consisting of (1) - (69) and (70):



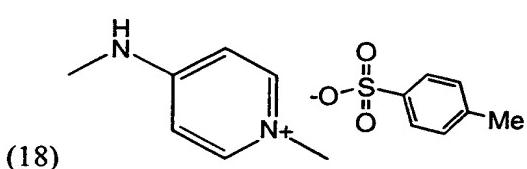
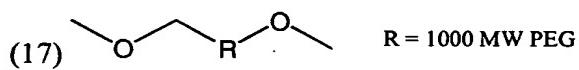




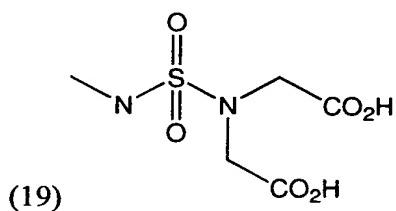
(15a)



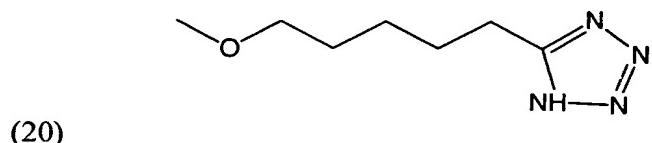
(16)



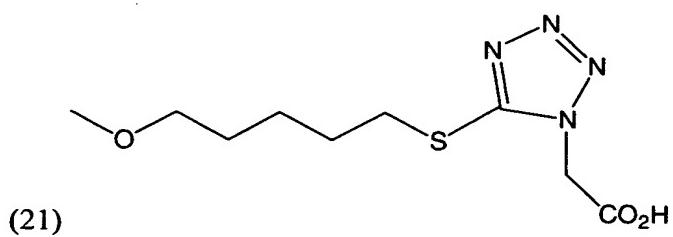
(18)

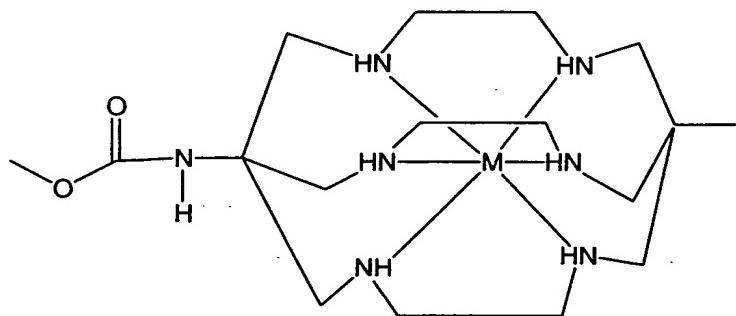
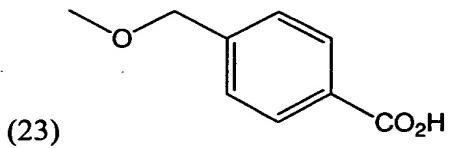
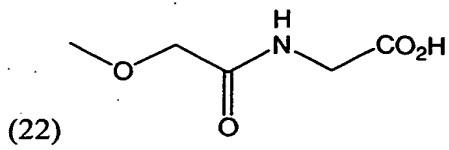


(19)

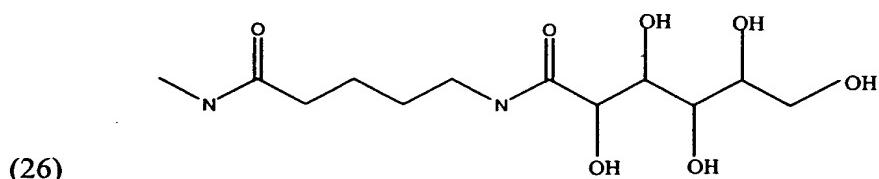
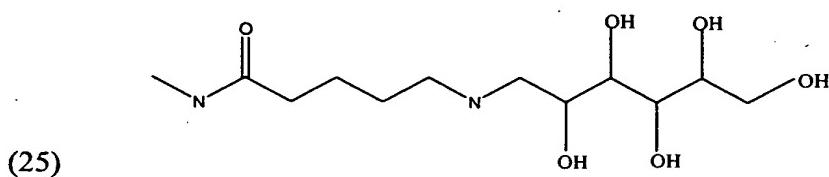


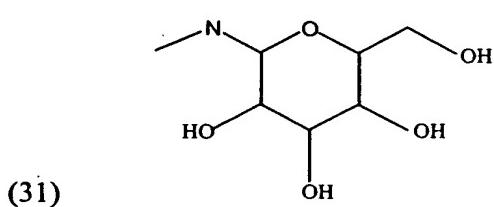
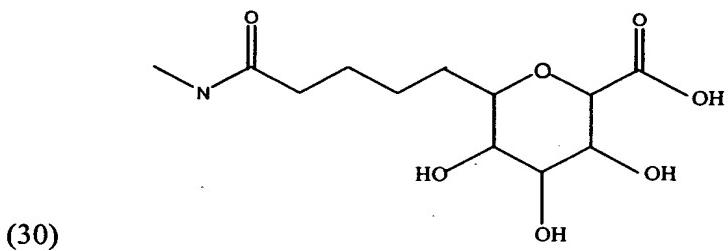
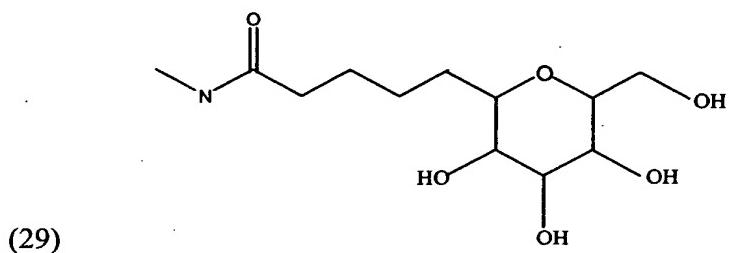
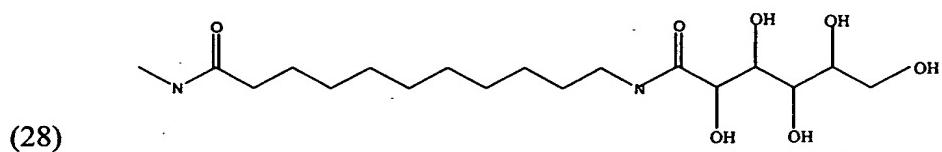
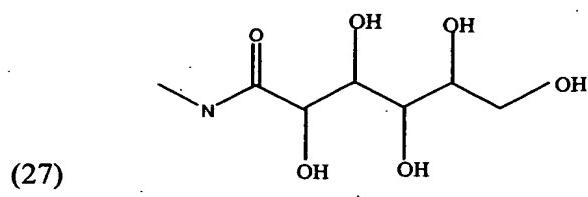
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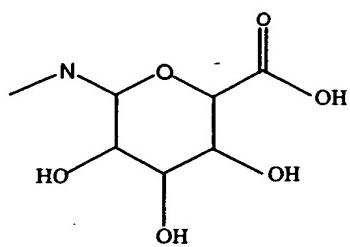




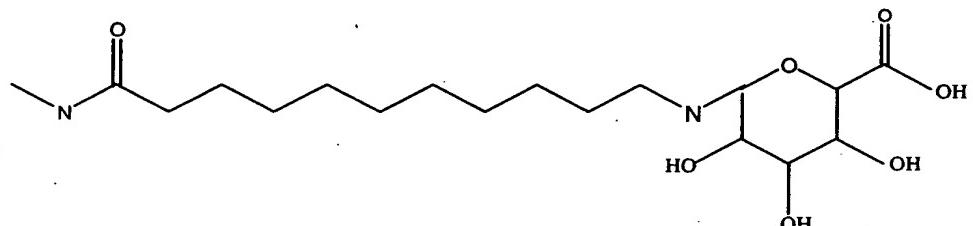
$$(24) \quad M = Co^{II, III}, Mn^{II, III}, Fe^{II, III}, Ni^{II, III}, Cr^{III}, Cu^{II}, Zn^{II}, Cd^{II}, Ga^{III}, In^{III}, V^{IV}, Ru^{II}, Pr^{IV}, Rh^{III} \text{ or Ir}^{III}$$



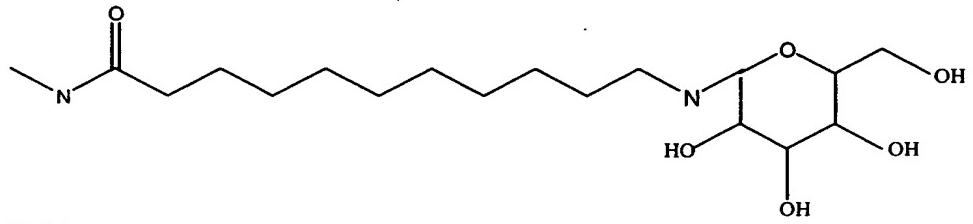




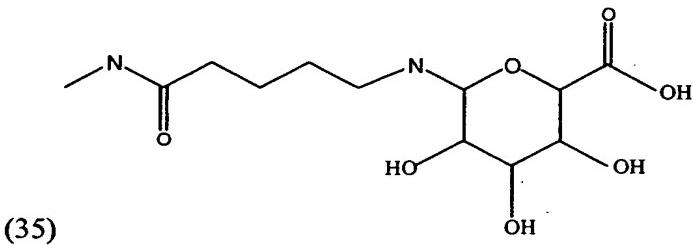
(32)



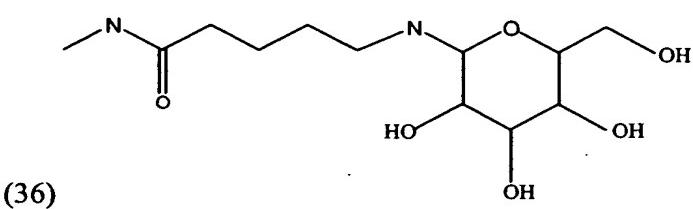
(33)



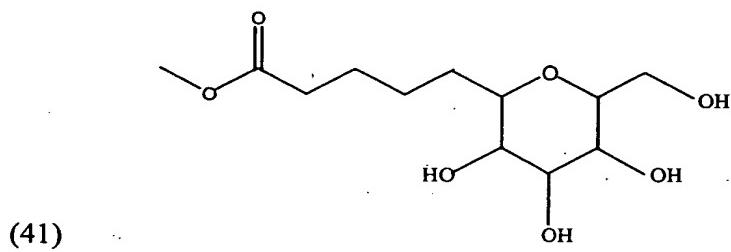
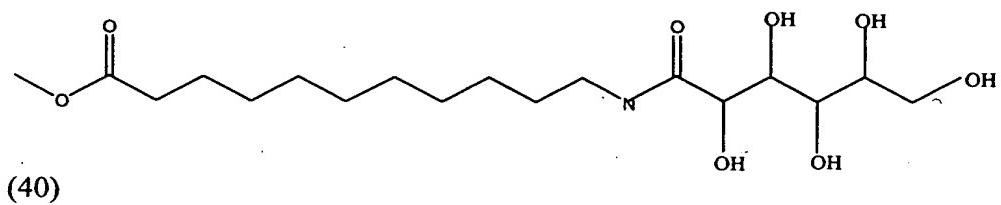
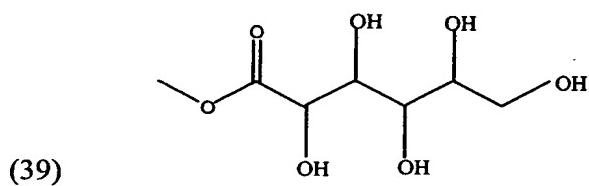
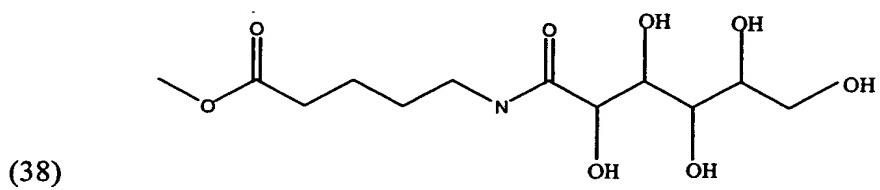
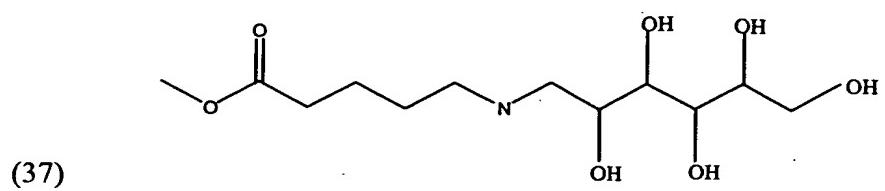
(34)

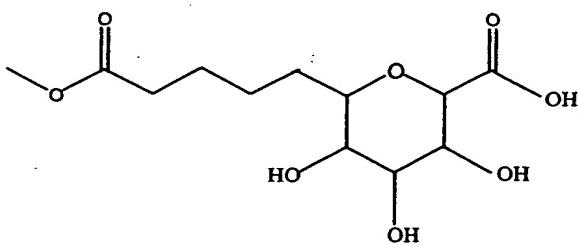


(35)

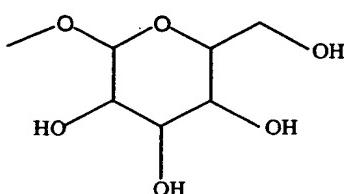


(36)

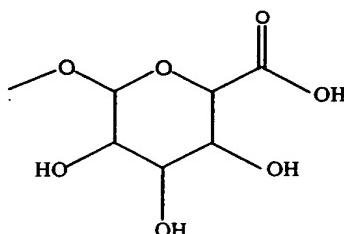




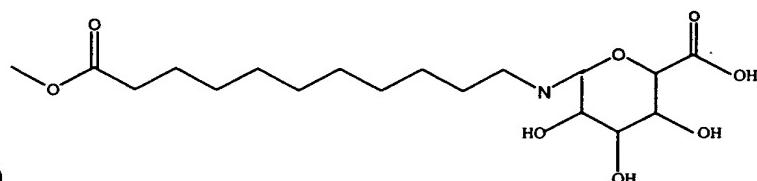
(42)



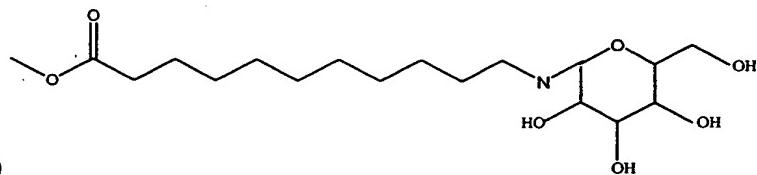
(43)



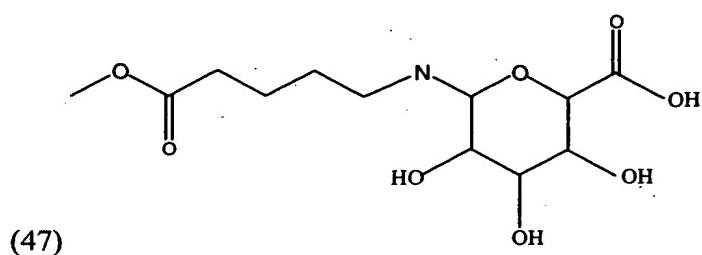
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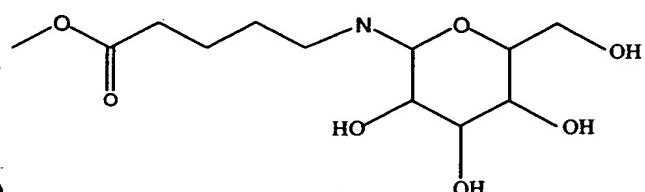
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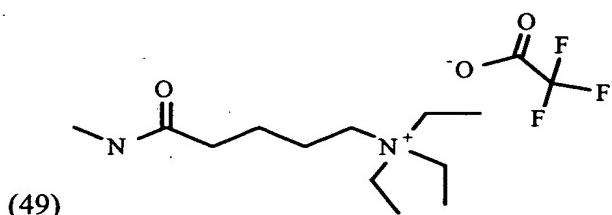
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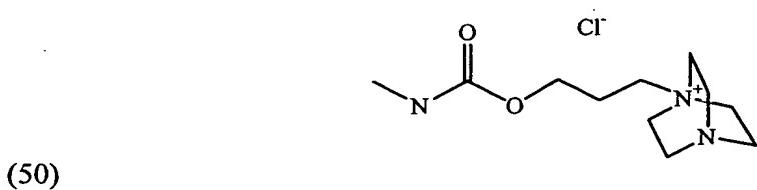
(47)



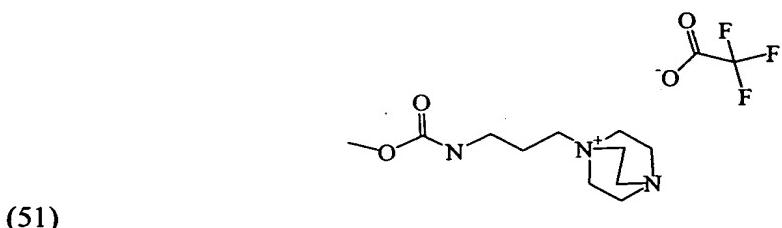
(48)



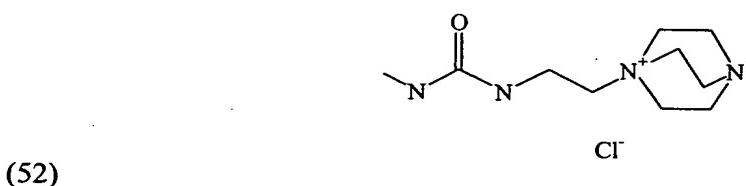
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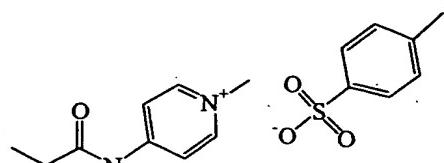
(50)



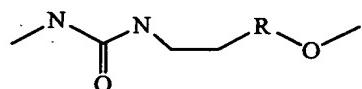
(51)



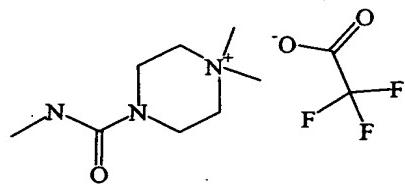
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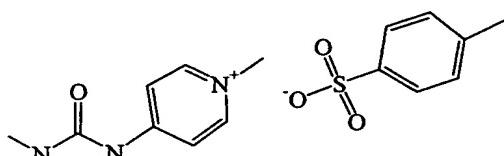
(53)



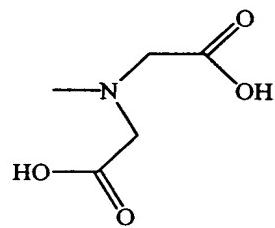
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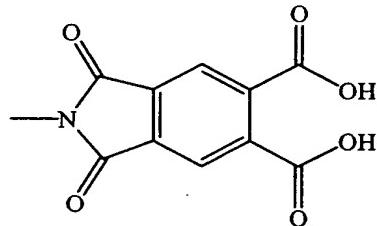
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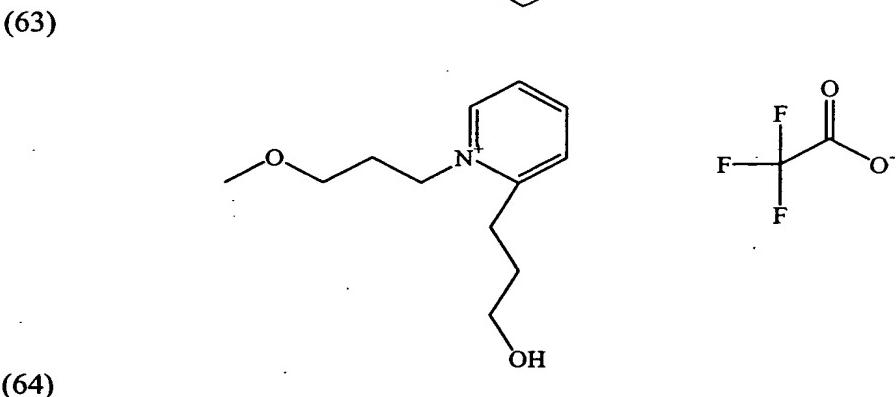
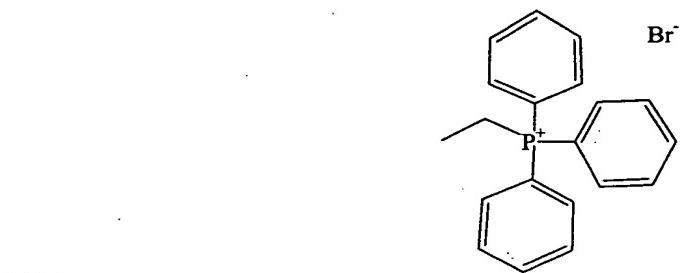
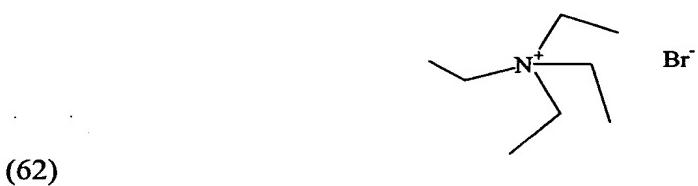
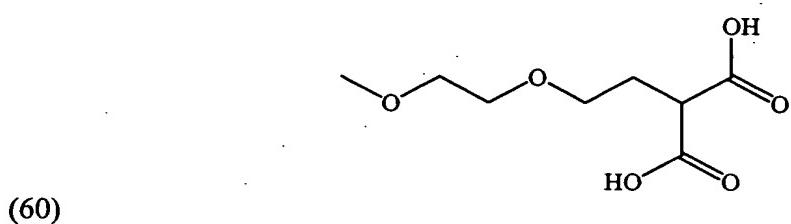
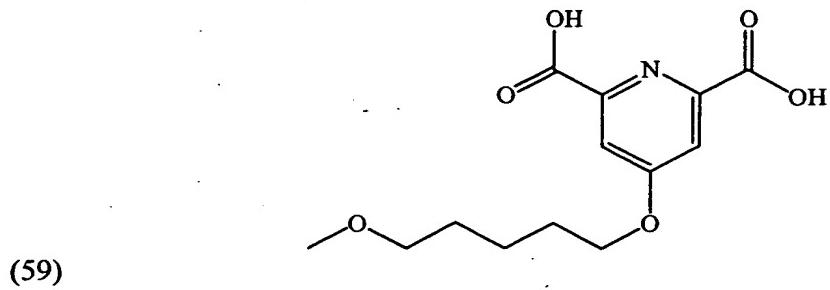
(56)

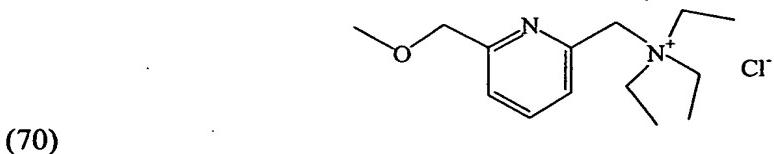
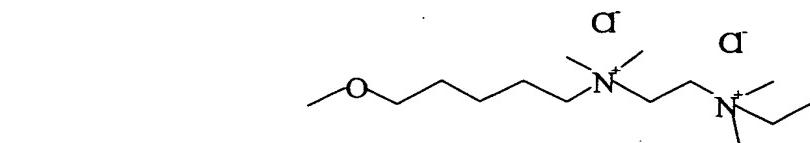
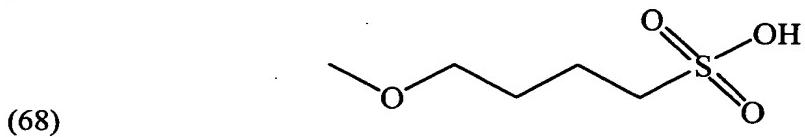
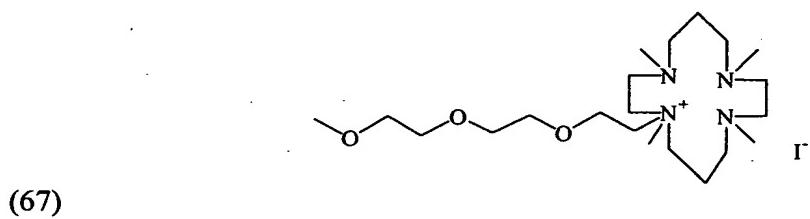
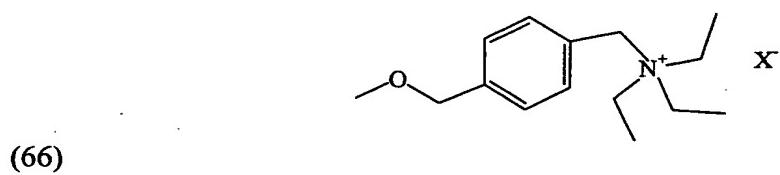
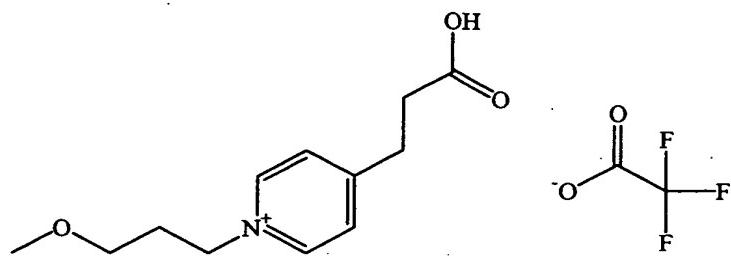


(57)



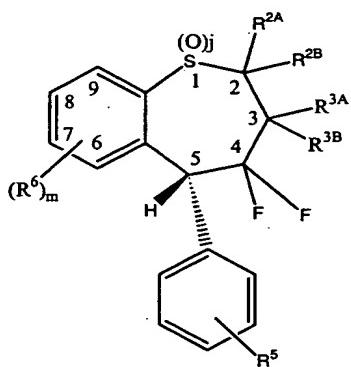
(58)



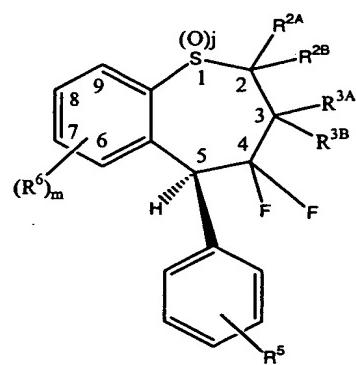


provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and R^{5B} is a right end of said R⁵ or vice versa.

[594] 130. The pharmaceutical composition of embodiment 129 wherein said compound of Formula I-17 comprises a member selected from the group consisting of Formulas I-21 and I-22 represented by:

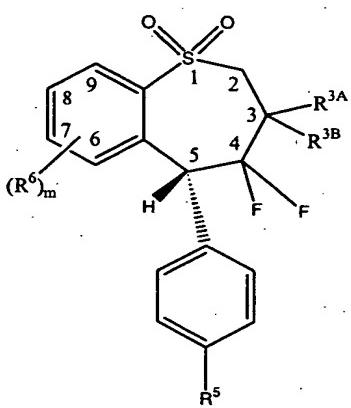


I-21

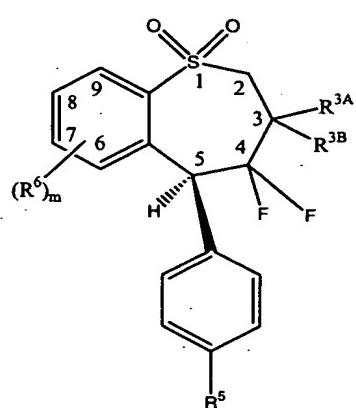


I-22.

[595] 131. The pharmaceutical composition of embodiment 130 wherein said compounds of Formulas I-21 and I-22 comprise Formulas I-9 and I-10, respectively, represented by:

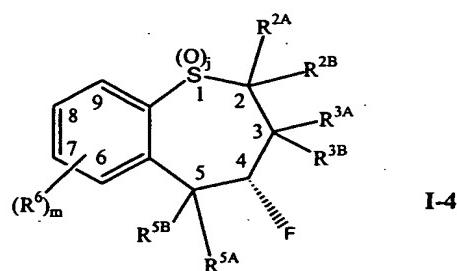
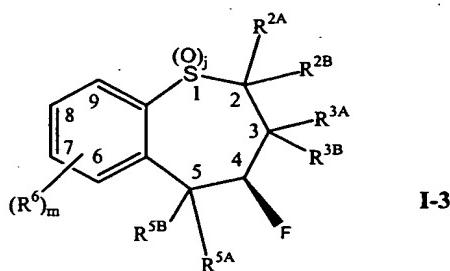


I-9

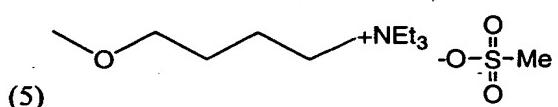
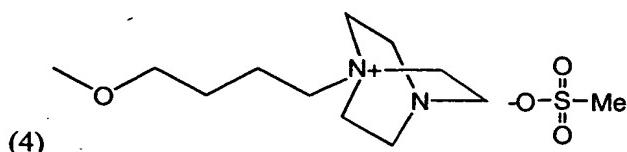
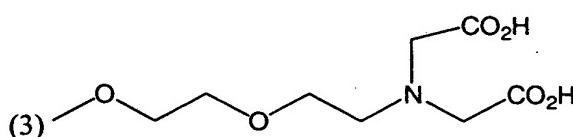
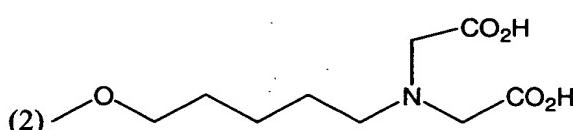
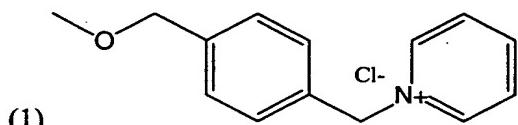


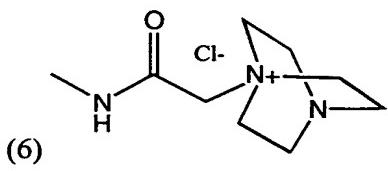
I-10.

[596] 132. The pharmaceutical composition of embodiment 128 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-3 and I-4 represented by:

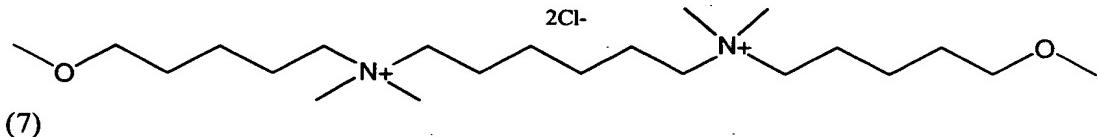


wherein R^{2A} , R^{2B} , R^{3A} , R^{3B} , R^{5A} , R^{5B} , R^6 , m and j are as previously defined and said R^5 is selected from the group consisting of (1) – (69) and (70):

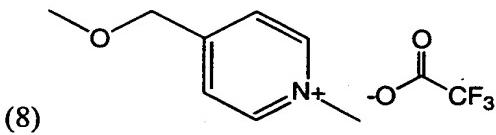




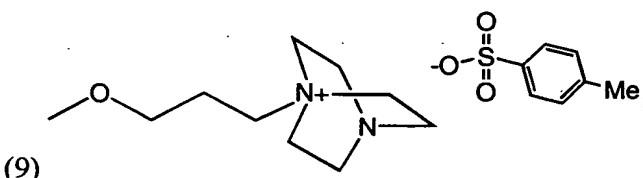
(6)



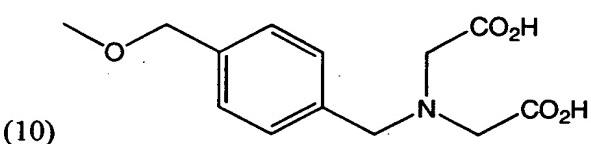
(7)



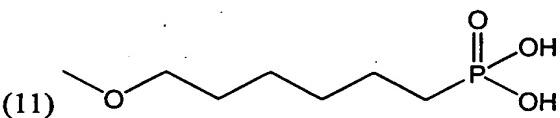
(8)



(9)



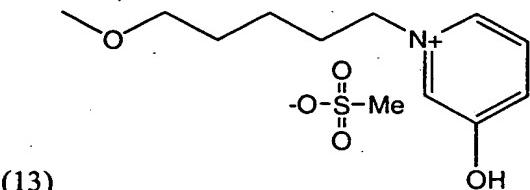
(10)



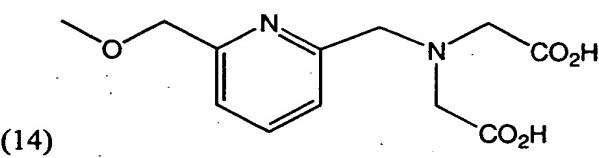
(11)



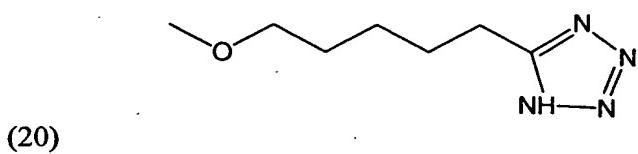
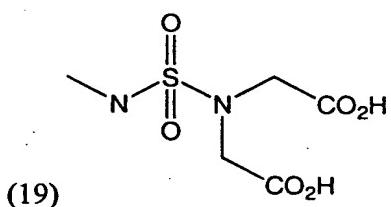
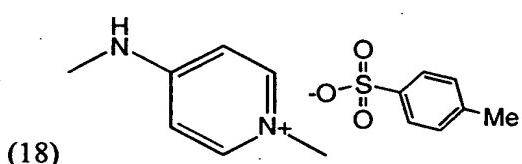
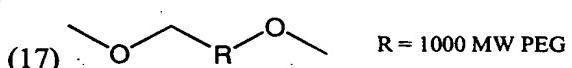
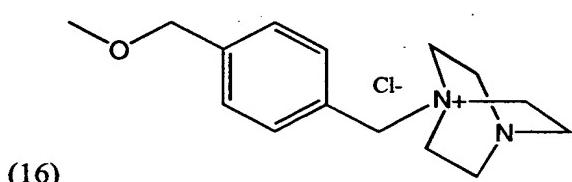
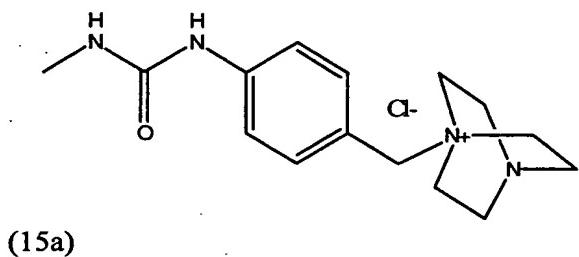
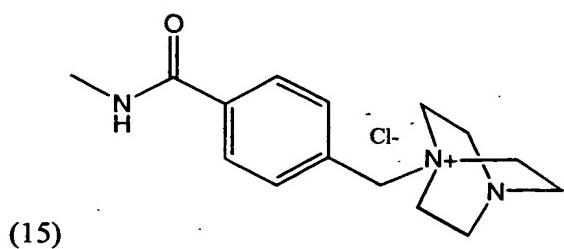
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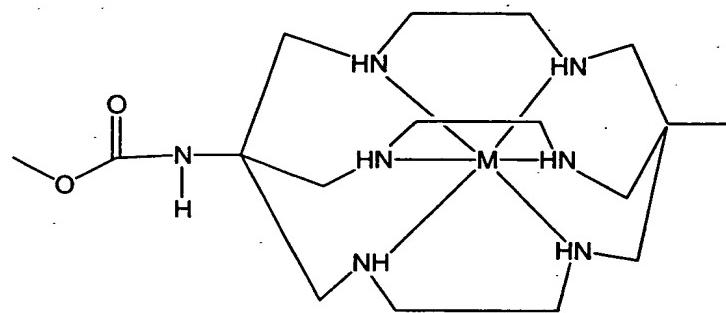
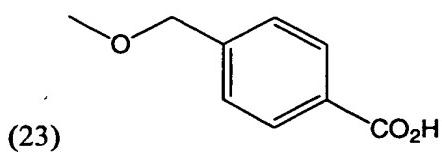
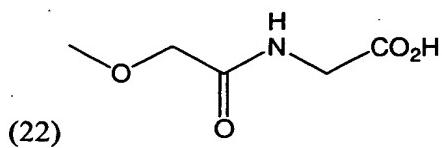
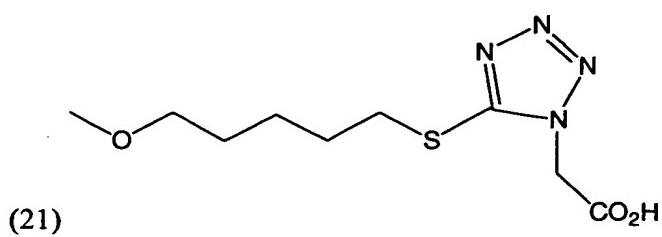


(13)

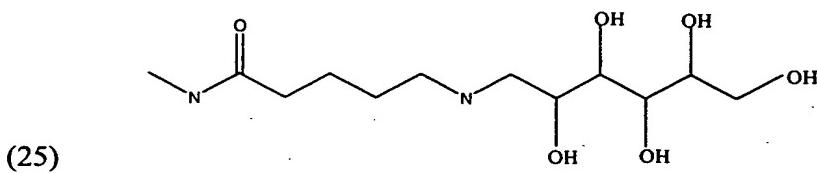


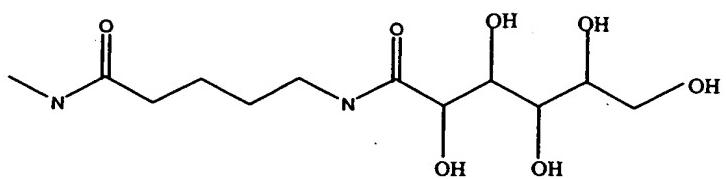
(14)



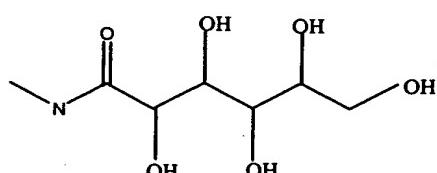


(24) $M = \text{Co}^{\text{II}}, \text{III}$, $\text{Mn}^{\text{II}}, \text{III}$, $\text{Fe}^{\text{II}}, \text{III}$, $\text{Ni}^{\text{II}}, \text{III}$,
 Cr^{III} , Cu^{II} , Zn^{II} , Cd^{II} , Ga^{III} , In^{III} , V^{IV} ,
 Ru^{II} , Pr^{IV} , Rh^{III} or Ir^{III}

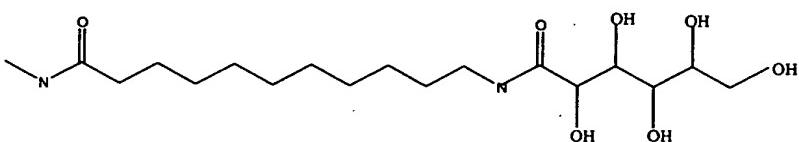




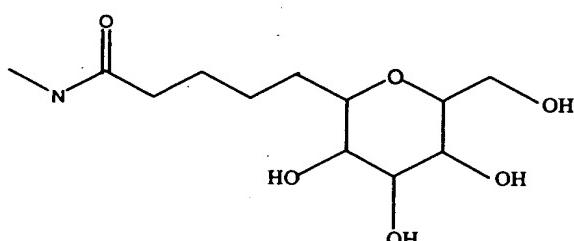
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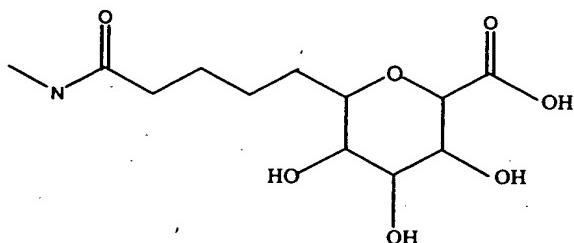
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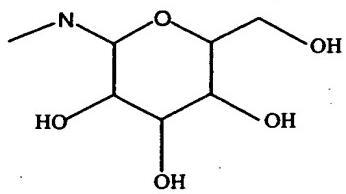
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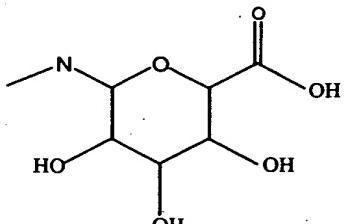
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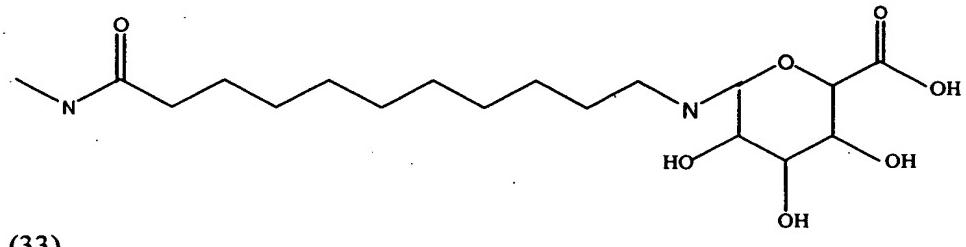
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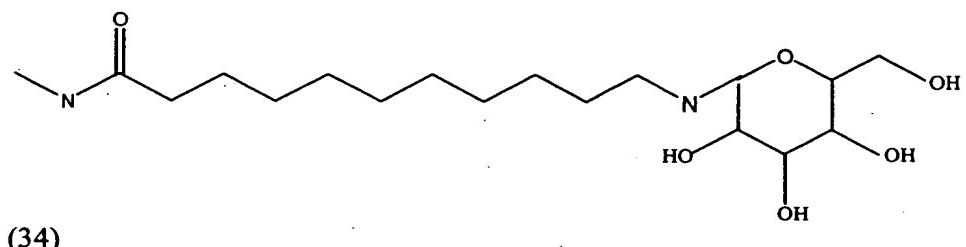
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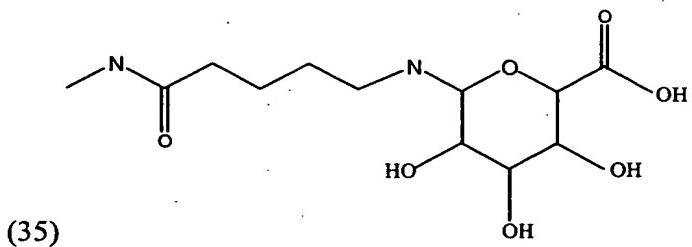
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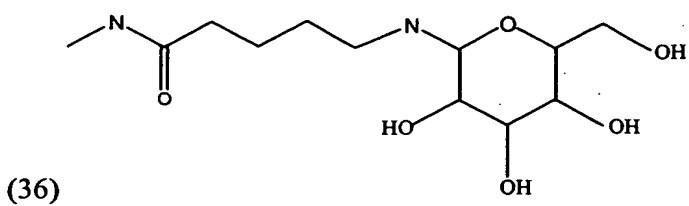
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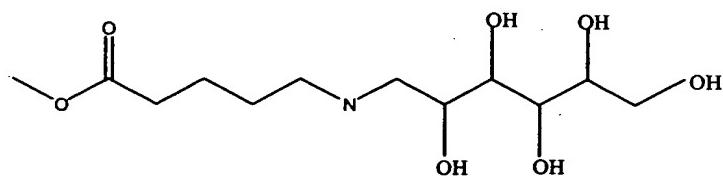
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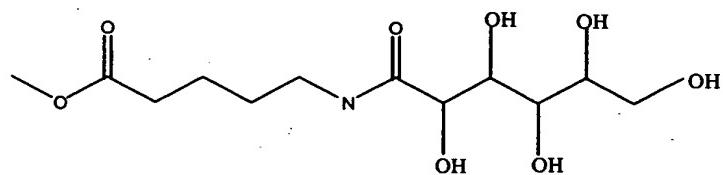
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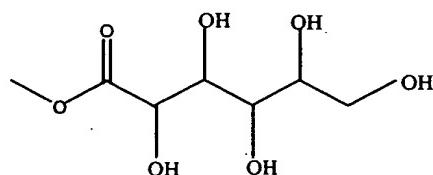
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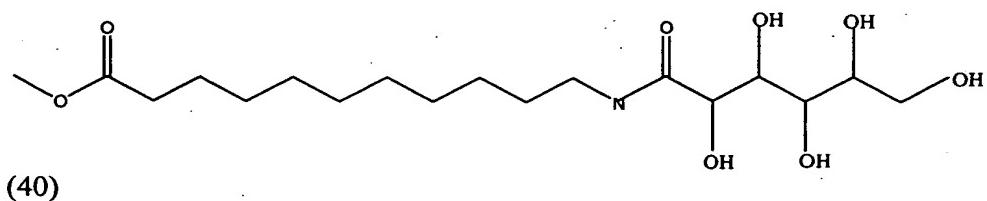
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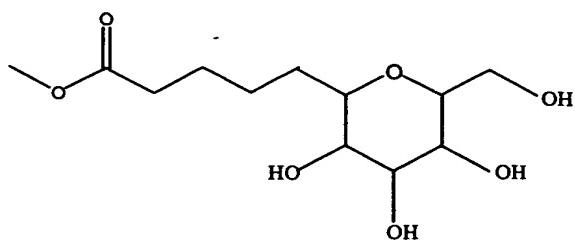
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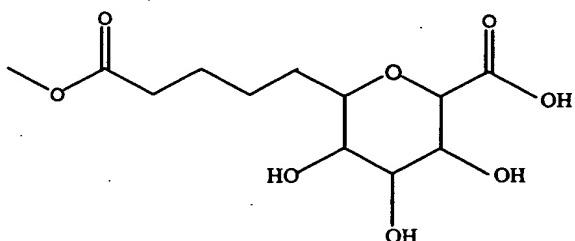
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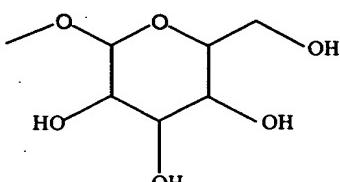
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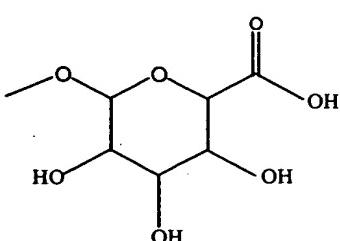
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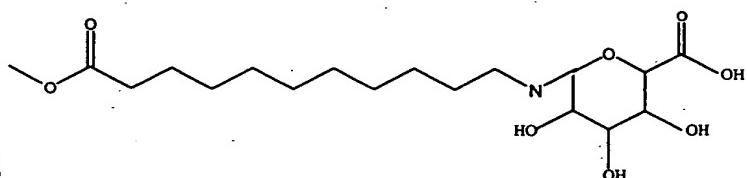
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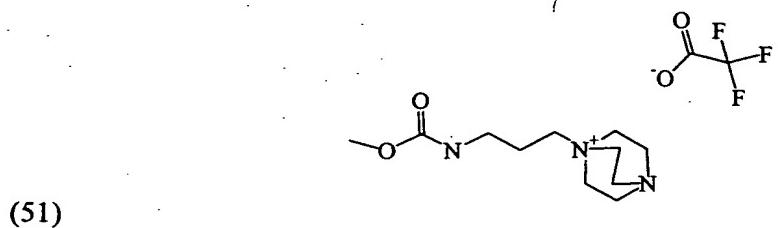
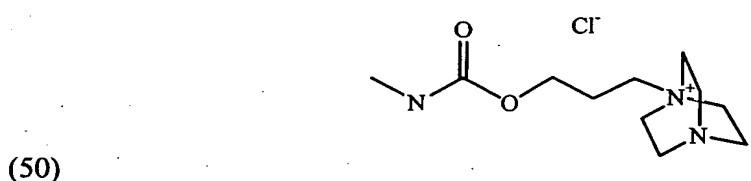
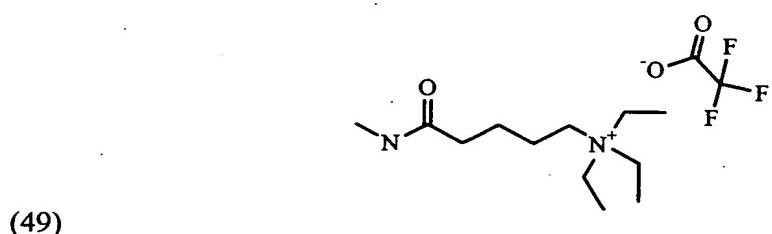
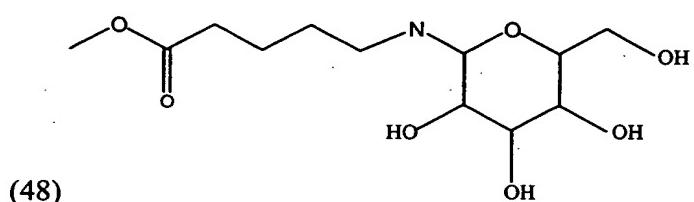
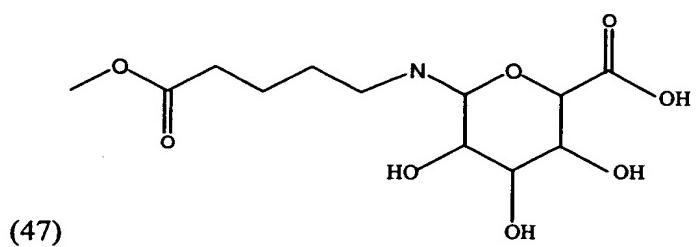
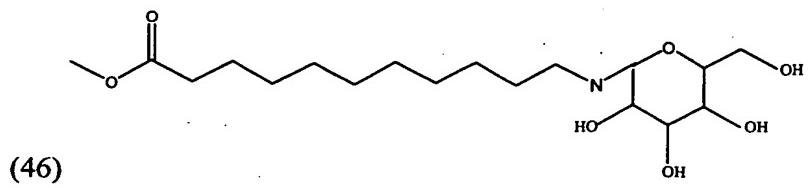
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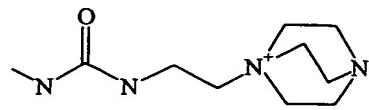


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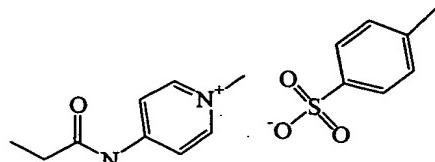


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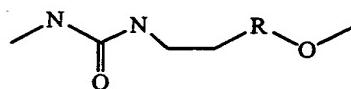




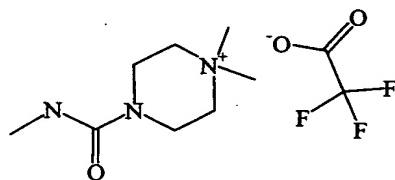
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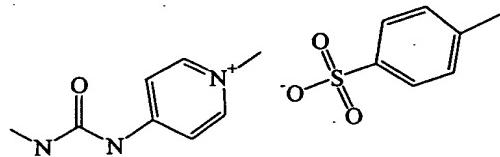
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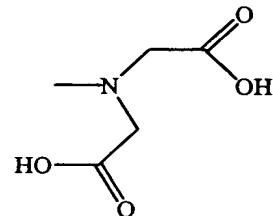
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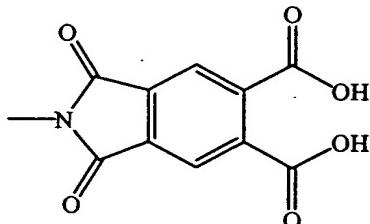
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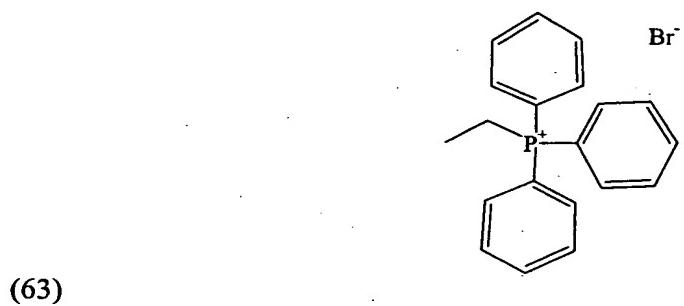
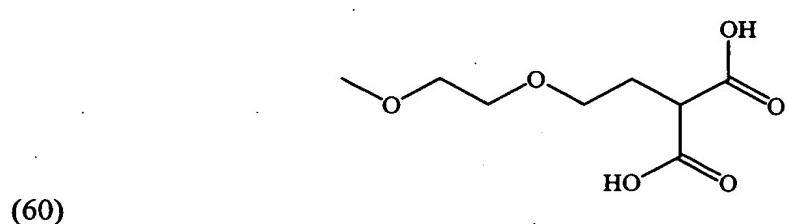
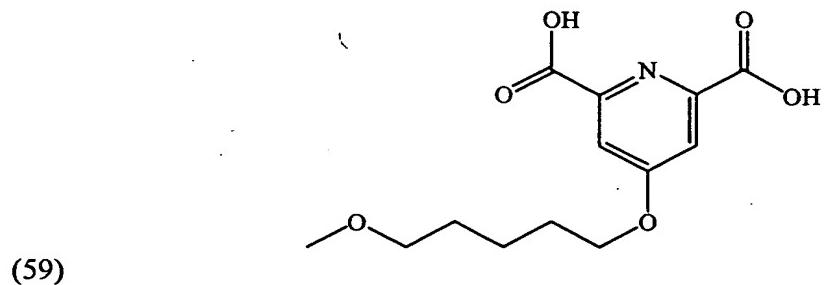
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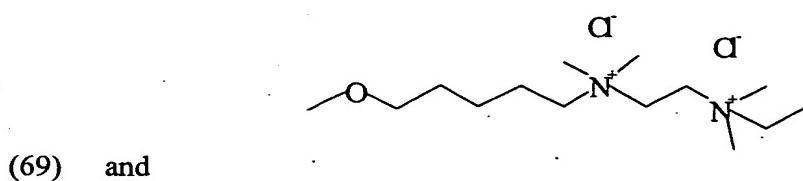
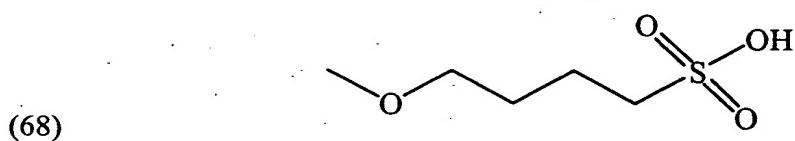
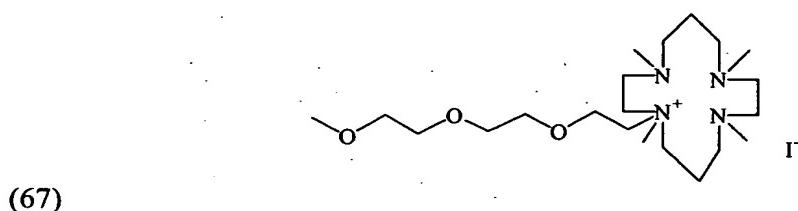
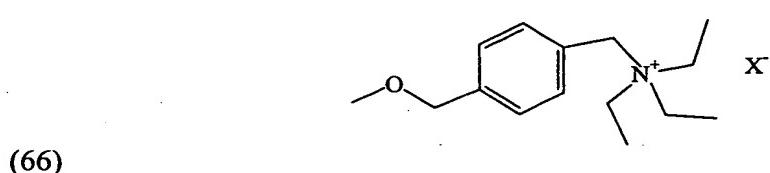
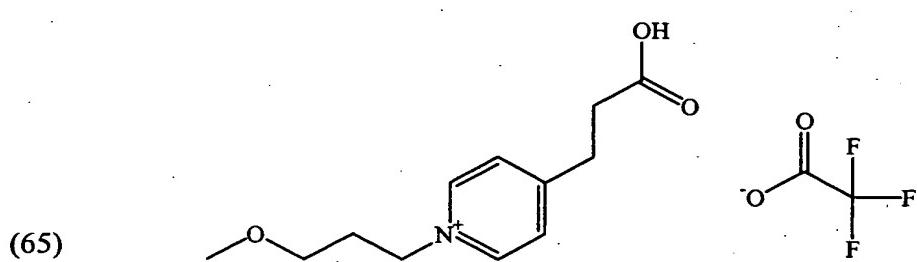
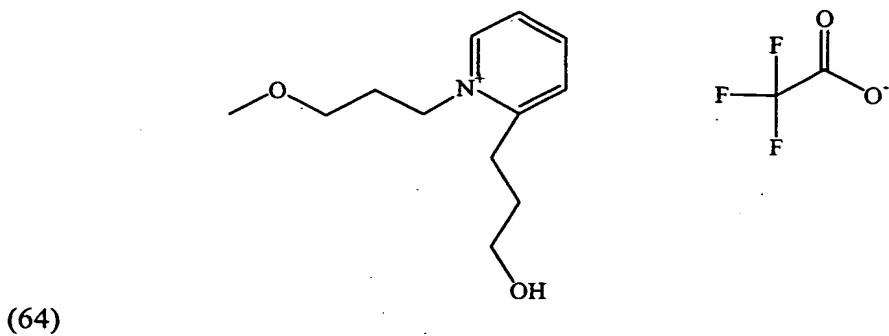


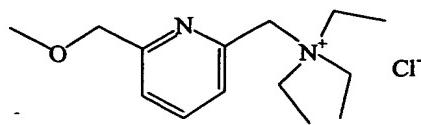
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(58)



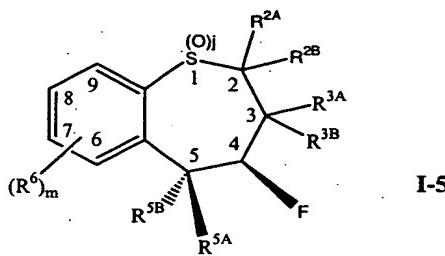




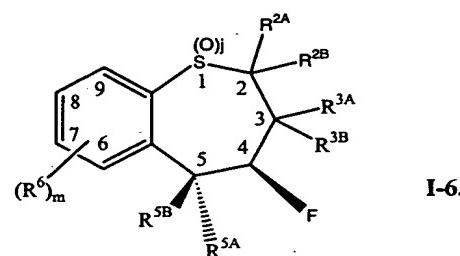
(70)

provided that when said R⁵ is (7), (17) or (24), then said R^{5A} is a left end of said R⁵ and said R^{5B} is a right end of said R⁵ or vice versa.

[597] 133. The pharmaceutical composition of embodiment 132 wherein said Formula I-3 comprises a member selected from the group consisting of Formulas I-5 and I-6 represented by:

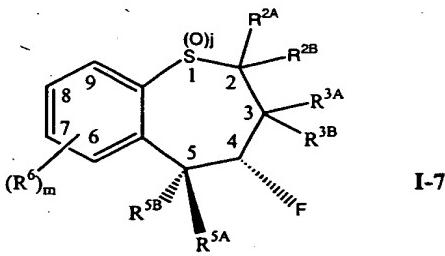


I-5

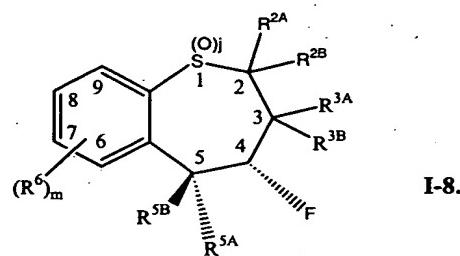


I-6.

[598] 134. The pharmaceutical composition of embodiment 132 wherein said Formula I-4 comprises a member selected from the group consisting of Formulas I-7 and I-8 represented by:

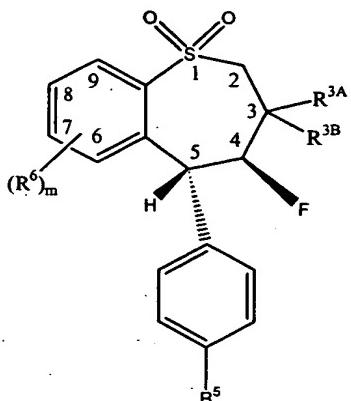


I-7

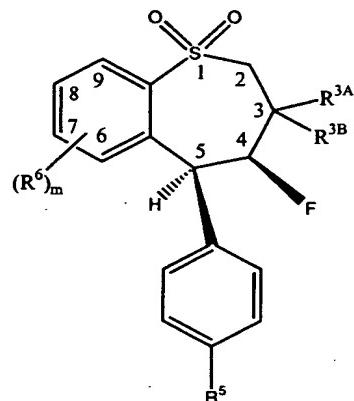


I-8.

[599] 135. The pharmaceutical composition of embodiment 133 wherein said compounds of Formulas I-6 and I-5 comprise Formulas I-13 and I-14, respectively, represented by:

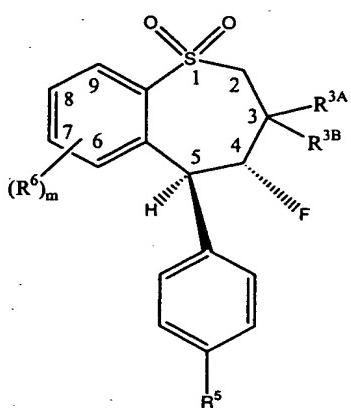


I-13

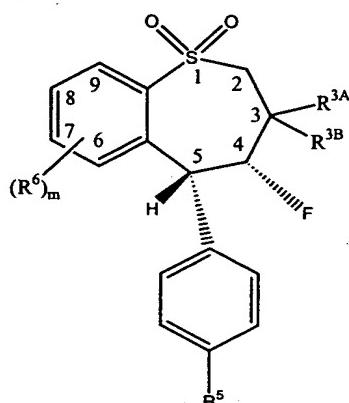


I-14.

[600] 136. The pharmaceutical composition of embodiment 134 wherein said compounds of Formulas I-7 and I-8 comprise Formulas I-15 and I-16, respectively, represented by:

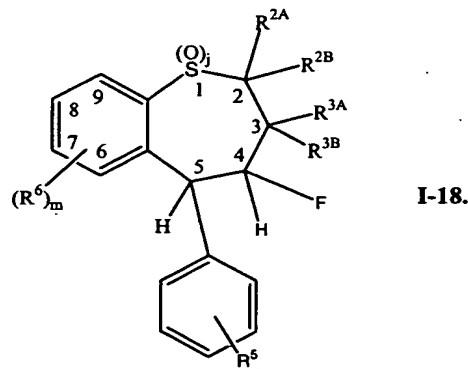


I-15



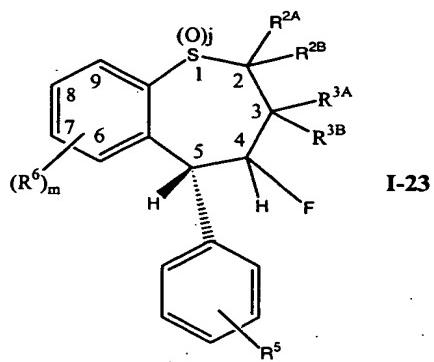
I-16.

[601] 137. The pharmaceutical composition of embodiment 128 wherein said compound of Formula I-2 comprises a compound of Formula I-18 represented by:

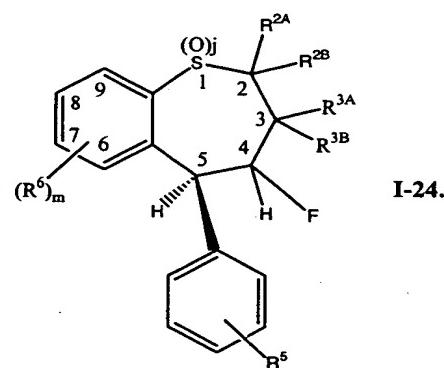


I-18.

- [602] 138. The pharmaceutical composition of embodiment 137 wherein said compound of Formula I-18 comprises a member selected from the group consisting of I-23 and I-24 represented by:

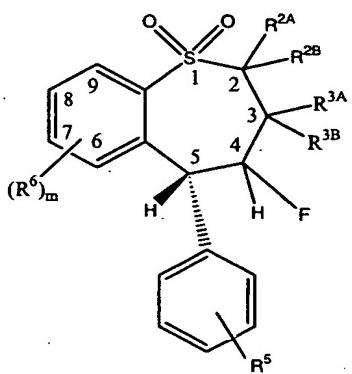


I-23

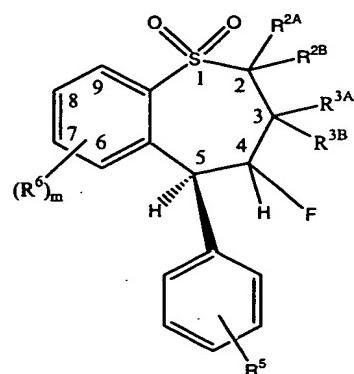


I-24.

- [603] 139. The pharmaceutical composition of embodiment 138 wherein said compounds of Formulas I-23 and I-24 comprise compounds of Formulas I-19 and I-20, respectively, represented by:

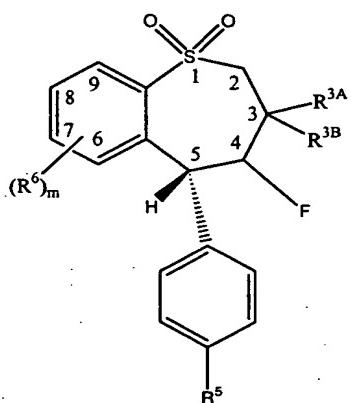


I-19

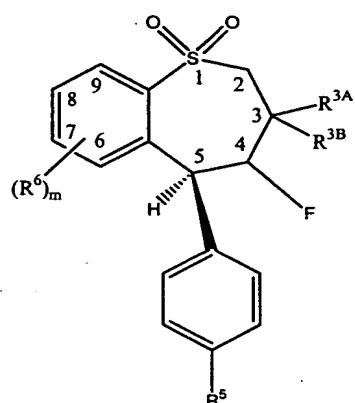


I-20.

[604] 140. The pharmaceutical composition of embodiment 128 wherein said compound of Formula I-2 is selected from the group consisting of Formulas I-11 and I-12 represented by:



I-11



I-12.

[605] 141. The pharmaceutical composition of embodiment 128 provided in a coated dosage form, said coated dosage form having a coating of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropylmethyl cellulose phthalate, or an anionic polymer of methacrylic acid and methacrylic acid methyl ester.

[606] 142. The compound of embodiment 1 provided in a coated dosage form, said coated dosage form having a coating of cellulose acetate phthalate,

polyvinylacetate phthalate, hydroxypropylmethyl cellulose phthalate, or an anionic polymer of methacrylic acid and methacrylic acid methyl ester.

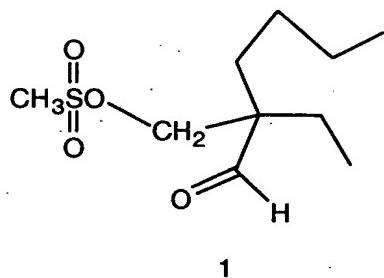
- [607] 143. The pharmaceutical composition of embodiment 128 provided in a dosage form selected from the group consisting of a tablet, a capsule, a suspension, an emulsion, a solution, a cream, a paste, a lotion, a suppository, or a powder.
- [608] 144. The pharmaceutical composition of embodiment 128 in a dosage form selected from the group consisting of a sublingual tablet, an effervescent tablet, and a coated tablet.
- [609] 145. The pharmaceutical composition of embodiment 128 provided in a dosage form comprising a slow release dosage form.
- [610] 146. The pharmaceutical composition of embodiment 145 wherein said slow release dosage form is selected from the group consisting of an implant or a coated tablet.
- [611] 147. The pharmaceutical composition of embodiment 146 wherein said solution, said suspension or said emulsion are suitable for parenteral administration to said subject.
- [612] 148. The pharmaceutical composition of embodiment 143 wherein said solution comprises a syrup.
- [613] 149. The pharmaceutical composition of embodiment 128 provided in a dosage form comprising a dispersion.
- [614] 150. The compound of embodiment 1 provided in a dosage form selected from the group consisting of a tablet, a capsule, a suspension, an emulsion, a solution, a cream, a paste, a lotion, a suppository, and a powder.

[615] EXAMPLES OF SYNTHETIC PROCEDURES

[616] The following examples use a numbering scheme for referring to the various compounds depicted below that may be different from the numbering scheme that is used in the earlier part of this patent application.

[617] Preparation 1

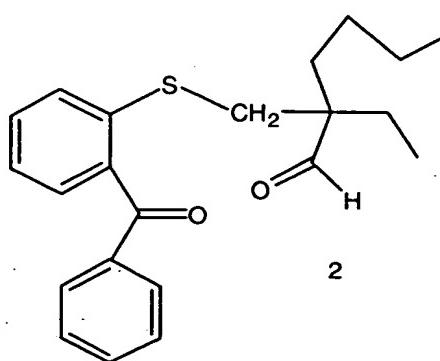
[618] 2-Ethyl-2-(mesyloxymethyl)hexanal (1)



[619] To a cold (10 °C) solution of 12.6 g (0.11 mole) of methanesulfonyl chloride and 10.3 g (0.13 mole) of triethylamine was added dropwise 15.8 g of 2-ethyl-2-(hydroxymethyl)hexanal, prepared according to the procedure described in Chem. Ber. 98, 728-734 (1965), while maintaining the reaction temperature below 30 °C. The reaction mixture was stirred at room temperature for 18 h, quenched with dilute HCl and extracted with methylene chloride. The methylene chloride extract was dried over MgSO₄ and concentrated in vacuo to give 24.4 g of brown oil.

[620] Preparation 2

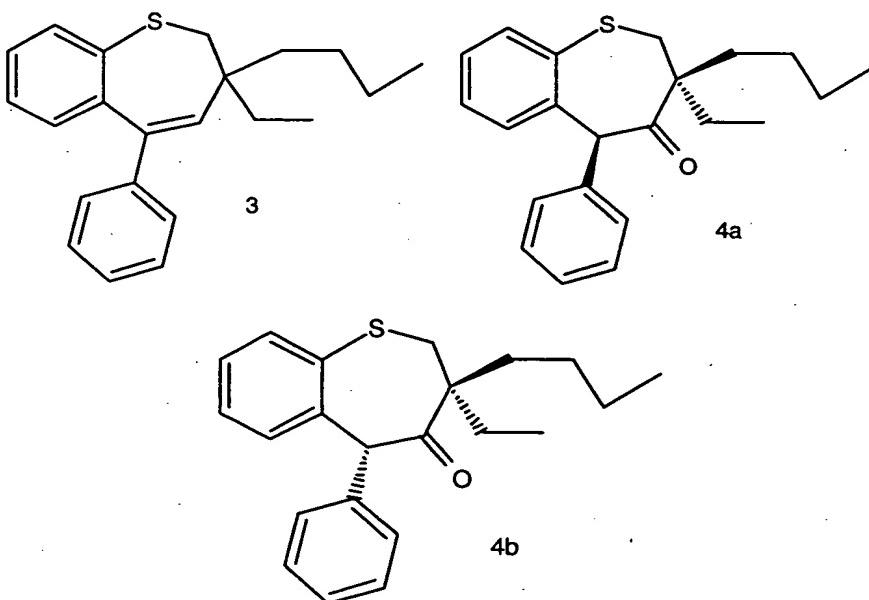
[621] 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (2)



[622] A mixture of 31 g (0.144 mol) of 2-mercaptobenzophenone, prepared according to the procedure described in WO 93/16055, 24.4 g (0.1 mole) of 2-ethyl-2-(mesyloxymethyl)-hexanal **1**, 14.8 g (0.146 mole) of triethylamine, and 80 mL of 2-methoxyethyl ether was held at reflux for 24 h. The reaction mixture was poured into 3N HCl and extracted with 300 mL of methylene chloride. The methylene chloride layer was washed with 300 mL of 10% NaOH, dried over MgSO₄ and concentrated in vacuo to remove 2-methoxyethyl ether. The residue was purified by HPLC (10% EtOAc-hexane) to give 20.5 g (58%) of **2** as an oil.

[623] Example 1

[624] **3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine (3), cis-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5H)4-one (4a) and trans-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5H)4-one (4b)**

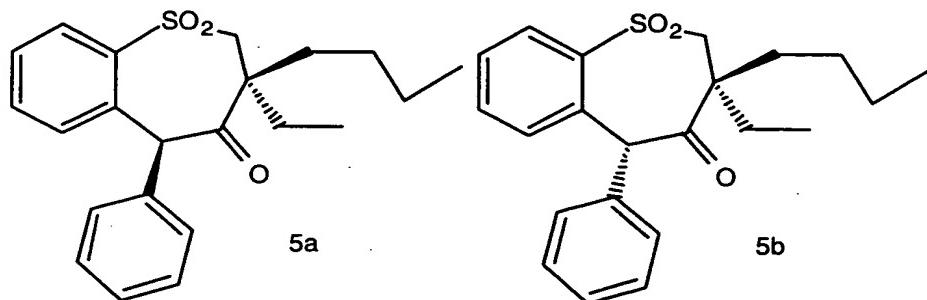


[625] A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of TiCl₃ and 80 mL of anhydrous ethylene glycol dimethyl ether (DME) was held at reflux for 2 h. The reaction mixture was cooled to 5 °C. To the reaction mixture was added dropwise a solution of 3.54 g (0.01 mole) of **2** in 30 mL of DME in 40 min. The reaction mixture was stirred at room temperature for 16 h and then was held at reflux for 2 h and cooled before being poured into brine. The organic was extract

into methylene chloride. The methylene chloride extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by HPLC (hexane) to give 1.7 g (43%) of **3** as an oil in the first fraction. The second fraction was discarded and the third fraction was further purified by HPLC (hexane) to give 0.07 g (2%) of **4a** in the earlier fraction and 0.1 g (3%) of **4b** in the later fraction.

[626] Example 2

- [627] *cis*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepin-(5*H*)-4-one-1,1-dioxide (**5a**) and *trans*-3-Butyl-3-ethyl-5-phenyl-2,3-dihydro-benzothiepin-(5*H*)-4-one-1,1-dioxide (**5b**)

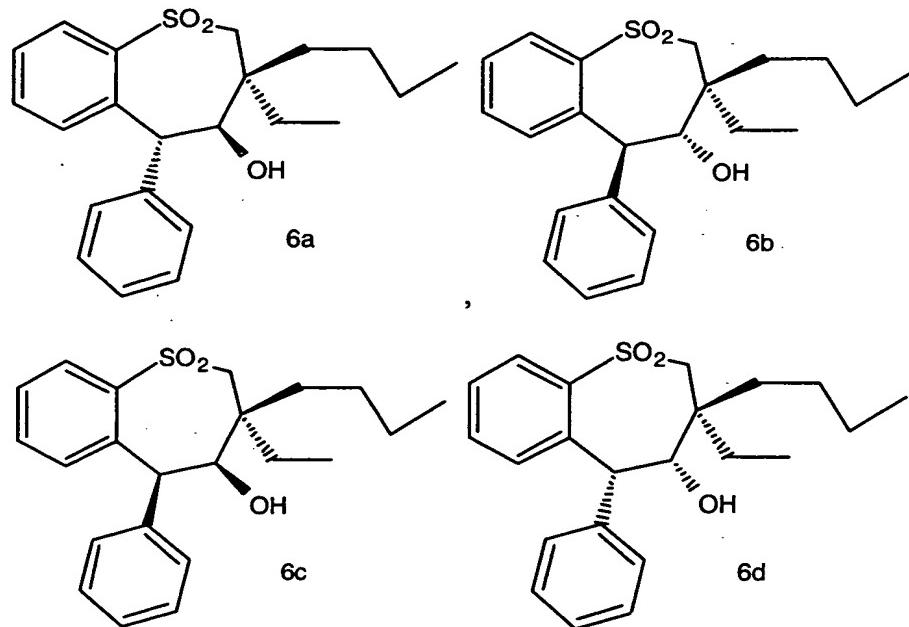


- [628] To a solution of 1.2 g (3.5 mmole) of 50-60% MCPBA in 20 mL of methylene chloride was added 0.59 g (1.75 mmole) of a mixture of **4a** and **4b** in 10 mL of methylene chloride. The reaction mixture was stirred for 20 h. An additional 1.2 g (1.75 mmole) of 50-60% MAPBA was added and the reaction mixture was stirred for an additional 3 h then was triturated with 50 mL of 10% NaOH. The insoluble solid was filtered. The methylene chloride layer of the filtrate was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual syrup was purified by HPLC (5% EtOAc-hexane) to give 0.2 g (30%) of **5a** as an oil in the first fraction and 0.17 g (26%) of **5b** as an oil in the second fraction.

[629] Example 3

- [630] ($3\alpha,4\alpha,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**6a**), ($3\alpha,4\beta,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepin-1,1-dioxide (**6b**),

($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydr xy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6c), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (6d)



[631] **A. Reduction of 5a and 5b with Sodium Borohydride**

- [632] To a solution of 0.22 g (0.59 mmole) of 5b in 10 mL of ethanol was added 0.24 g (6.4 mmole) of sodium borohydride. The reaction mixture was stirred at room temperature for 18 h and concentrated in vacuo to remove ethanol. The residue was triturated with water and extracted with methylene chloride. The methylene chloride extract was dried over MgSO_4 and concentrated in vacuo to give 0.2 g of syrup. In a separate experiment, 0.45 g of 5a was treated with 0.44 g of sodium borohydride in 10 mL of ethanol and was worked up as described above to give 0.5 g of syrup which was identical to the 0.2 g of syrup obtained above. These two materials were combined and purified by HPLC using 10% EtOAc-hexane as eluant. The first fraction was 0.18 g (27%) of 6a as a syrup. The second fraction was 0.2 g (30%) of 6b also as a syrup. The column was then eluted with 20% EtOAc-hexane to give 0.077 g (11%) of 6c in the third fraction as a solid. Recrystallization from hexane gave a solid, mp 179-181 °C. Finally, the column

was eluted with 30% EtOAc-hexane to give 0.08 g (12%) of 6d in the fourth fraction as a solid. Recrystallization from hexane gave a solid, mp 160-161 °C.

[633] **B. Conversion of 6a to 6c and 6d with NaOH and PTC**

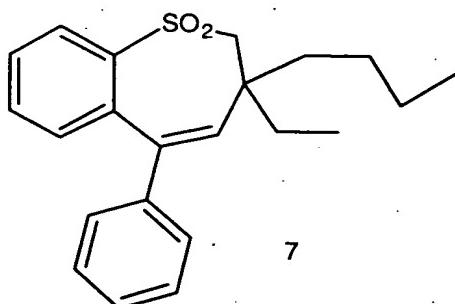
[634] To a solution of 0.29 g (0.78 mmole) of 6a in 10 mL CH₂Cl₂, was added 9 g of 40% NaOH. The reaction mixture was stirred for 0.5 h at room temperature and was added one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst (PTC). The mixture was stirred for 0.5 h at room temperature before being treated with 25 mL of ice-crystals then was extracted with CH₂Cl₂ (3x10 ml), dried over MgSO₄ and concentrated in vacuo to recover 0.17 g of a colorless film. The components of this mixture were separated using an HPLC and eluted with EtOAc-hexane to give 12.8 mg (4%) of 2-(2-benzylphenylsulfonylmethyl)-2-ethylhexenal in the first fraction, 30.9 mg (11%) of 6c in the second fraction and 90.0 mg (31%) of 6d in the third fraction.

[635] **Oxidation of 6a to 5b**

[636] To a solution of 0.20 g (0.52 mmole) of 6a in 5 mL of CH₂Cl₂ was added 0.23 g (1.0 mmole) of pyridinium chlorochromate. The reaction mixture was stirred for 2 h then was treated with additional 0.23 g of pyridinium chlorochromate and stirred overnight. The dark reaction mixture was poured into a ceramic filterfrit containing silica gel and was eluted with CH₂Cl₂. The filtrate was concentrated in vacuo to recover 167 mg (87%) of 5b as a colorless oil.

[637] Example 4

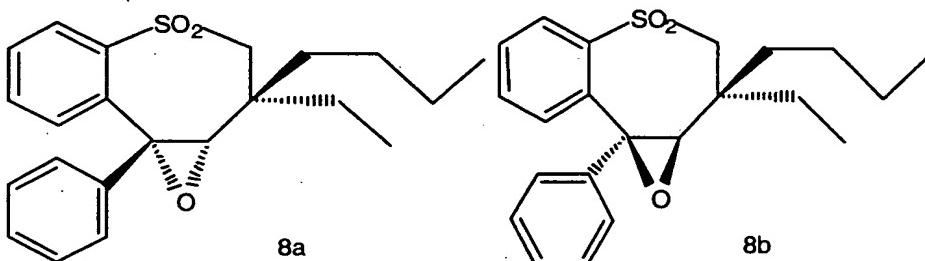
[638] **3-Butyl-3-ethyl-5-phenyl-2,3-dihydrobenzothiepine-1,1-dioxide (7)**



[639] To a solution of 5.13 g (15.9 mmole) of **3** in 50 mL of CH₂Cl₂ was added 10 g (31.9 mmole) of 50-60% MCPBA (m-chloroperoxybenzoic acid) portionwise causing a mild reflux and formation of a white solid. The reaction mixture was allowed to stir overnight under N₂ and was triturated with 25 mL of water followed by 50 mL of 10% NaOH solution. The organic was extracted into CH₂Cl₂ (4x20 mL). The CH₂Cl₂ extract was dried over MgSO₄ and evaporated to dryness to recover 4.9 g (87%) of an opaque viscous oil.

[640] Example 5

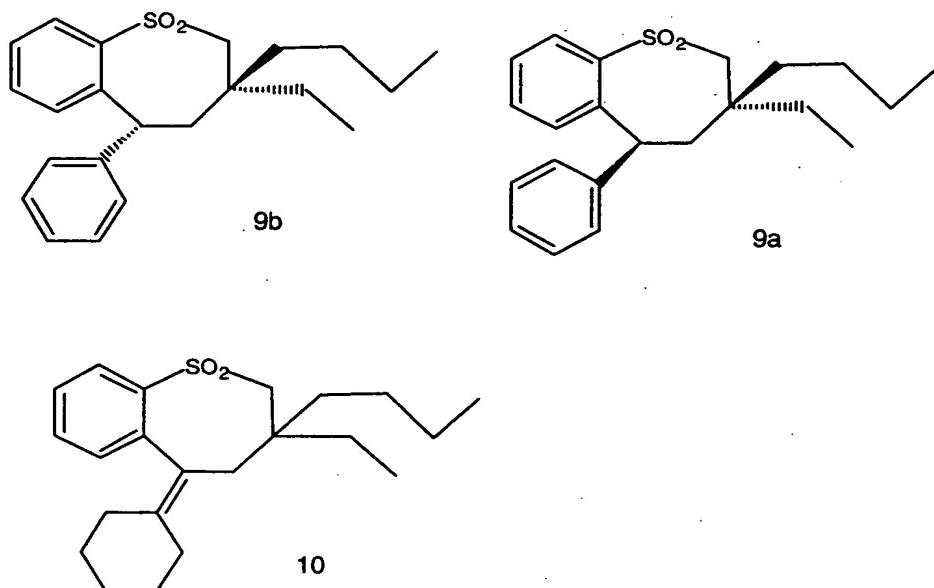
[641] (*1a* α ,*2* β ,*8b* α) 2-Butyl-2-ethyl-8b-phenyl-1*a*,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (**8a**) (*1a* α ,*2* α ,*8b* α) 2-Butyl-2-ethyl-8b-phenyl-1*a*,2,3,8b-tetrahydro-benzothiepino[4,5-*b*]oxirene-4,4-dioxide (**8b**)



[642] To 1.3 g (4.03 mole) of **3** in 25 mL of CHCl₃ was added portionwise 5 g (14.1 mmole) of 50-60 % MCPBA causing a mild exotherm. The reaction mixture was stirred under N₂ overnight and was then held at reflux for 3 h. The insoluble white slurry was filtered. The filtrate was extracted with 10% potassium carbonate (3x50 mL), once with brine, dried over MgSO₄, and concentrated in vacuo to give 1.37 g of a light yellow oil. Purification by HPLC gave 0.65 g of crystalline product. This product is a mixture of two isomers. Trituration of this crystalline product in hexane recovered 141.7 mg (10%) of a white crystalline product. This isomer was characterized by NMR and mass spectra to be the (*1a* α ,*2* β ,*8b* α) isomer **8a**. The hexane filtrate was concentrated in vacuo to give 206 mg of white film which is a mixture of 30% **8a** and 70% **8b** by ¹H NMR.

[643] Example 6

- [644] **cis-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (9a), trans-3-Butyl-3-ethyl-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (9b), and 3-Butyl-3-ethyl-4-hydroxy-5-cyclohexylidene-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (10)**



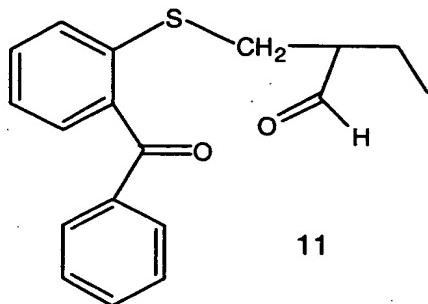
- [645] A mixture of 0.15 g (0.4 mmole) of a 3:7 mixture of **8a** and **8b** was dissolved in 15 ml MeOH in a 3 oz. Fisher/Porter vessel, then was added 0.1 g of 10% Pd/C catalyst. This mixture was hydrogenated at 70 psi H₂ for 5 h and filtered. The filtrate was evaporated to dryness in vacuo to recover 0.117 g of a colorless oil. This material was purified by HPLC eluting with EtOAc-hexane. The first fraction was 4.2 mg (3%) of **9b**. The second fraction, 5.0 mg (4%), was a 50/50 mixture of **9a** and **9b**. The third fraction was 8.8 mg (6%) of **6a**. The fourth fraction was 25.5 mg (18%) of **6b**. The fifth fraction was 9.6 mg (7%) of a mixture of **6b** and a product believed to be 3-butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide based on mass spectrum. The sixth fraction was 7.5 mg (5%) of a mixture of **6d** and one of the isomers of **10, 10a**.

[646] Example 7

[647] In another experiment, a product (3.7 g) from epoxidation of **3** with excess MCPBA in refluxing CHCl₃ under air was hydrogenated in 100 mL of methanol using 1 g of 10% Pd/C catalyst and 70 psi hydrogen. The product was purified by HPLC to give 0.9 g (25%) of **9b**, 0.45 g (13%) of **9a**, 0.27 g (7%) of **6a**, 0.51 g (14%) of **6b**, 0.02 g (1%) of **6c**, 0.06 g (2%) of one isomer of **10**, **10a** and 0.03 g (1%) of another isomer of **10**, **10b**.

[648] Example 8

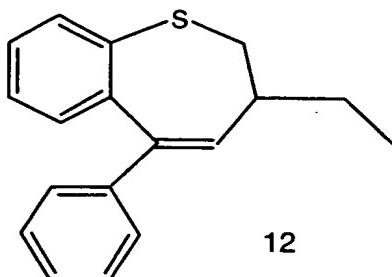
[649] 2-((2-Benzoylphenylthio)methyl)butyraldehyde (**11**)



[650] To an ice bath cooled solution of 9.76 g (0.116 mole) of 2-ethylacrolein in 40 mL of dry THF was added 24.6 g (0.116 mole) of 2-mercaptopbenzophenone in 40 mL of THF followed by 13 g (0.128 mole) of triethylamine. The reaction mixture was stirred at room temperature for 3 days, diluted with ether, and was washed successively with dilute HCl, brine, and 1 M potassium carbonate. The ether layer was dried over MgSO₄ and concentrated in vacuo. The residue was purified by HPLC (10% EtOAc-hexane) to give 22 g (64%) of **11** in the second fraction. An attempt to further purify this material by kugelrohr distillation at 0.5 torr (160-190 °C) gave a fraction (12.2 g) which contained starting material indicating a reversed reaction during distillation. This material was dissolved in ether (100 mL) and was washed with 50 mL of 1 M potassium carbonate three times to give 6.0 g of a syrup which was purified by HPLC (10% EtOAc-hexane) to give 5.6 g of pure **11**.

Example 9

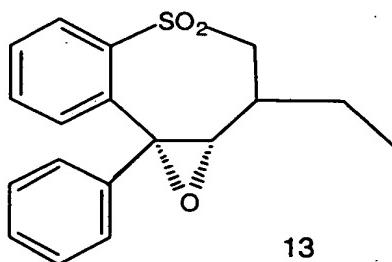
[651] 3-Ethyl-5-phenyl-2,3-dihydrobenzothiepine (12)



[652] To a mixture of 2.61 g (0.04 mole) of zinc dust and 60 mL of DME was added 7.5 g (0.048 mole) of $TiCl_3$. The reaction mixture was held at reflux for 2 h. A solution of 2.98 g (0.01 mole) of 11 was added dropwise in 1 h. The reaction mixture was held at reflux for 18 h, cooled and poured into water. The organic was extracted into ether. The ether layer was washed with brine and filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated. The residual oil (2.5 g) was purified by HPLC to give 2.06 g (77%) of 12 as an oil in the second fraction.

[653] Example 10

[654] ($1a\alpha,2\alpha,8b\alpha$) 2-Ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino-[4,5-*b*]oxirene-4,4-dioxide (13)

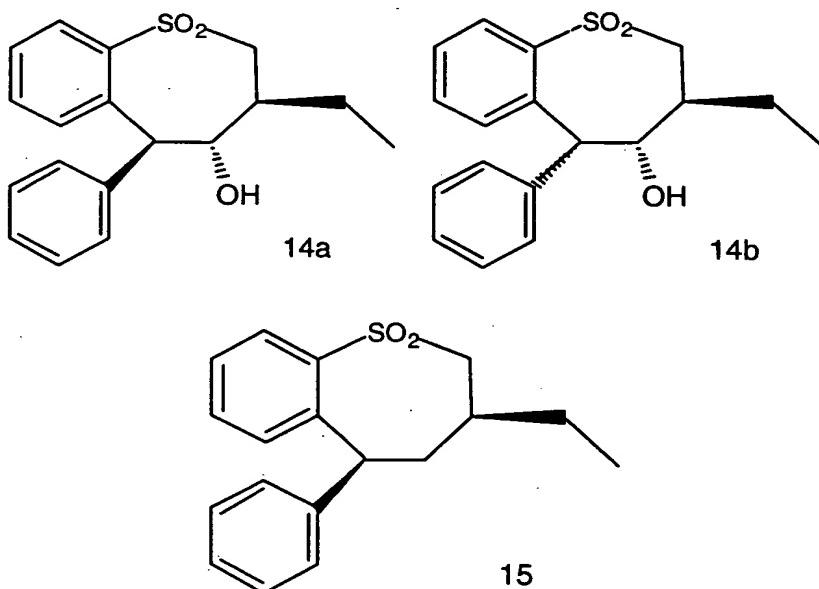


[655] To a solution of 1.5 g (5.64 mmole) of 12 in 25 ml of $CHCl_3$ was added 6.8 g (19.4 mmole) of 50-60% MCPB portionwise causing an exotherm and formation of a white solid. The mixture was stirred at room temperature overnight diluted with 100 ml methylene chloride and washed successively with 10% K_2CO_3 (4x50 ml),

water (twice with 25 ml) and brine. The organic layer was then dried over MgSO₄ and evaporated to dryness to recover 1.47 g of an off white solid. ¹H NMR indicated that only one isomer is present. This solid was slurried in 200 ml of warm Et₂O and filtered to give 0.82 g (46%) of 13 as a white solid, mp 185-186.5 °C.

[656] Example 11

- [657] (*3α,4β,5α*)-3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (14a), (*3α,4β,5β*) 3-Ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (14b), and *cis*-3-Ethyl-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (15)

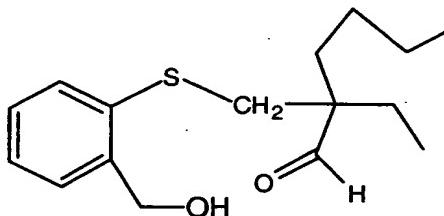


- [658] A mixture of 0.5 g (1.6 mole) of 13, 50 ml of acetic acid and 0.5 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 4 h. The crude reaction slurry was filtered and the filtrate was stirred with 150 ml of a saturated NaHCO₃ solution followed by 89 g of NaHCO₃ powder portionwise to neutralize the rest of acetic acid. The mixture was extracted with methylene chloride (4x25 ml), then the organic layer was dried over MgSO₄ and concentrated in vacuo to give 0.44 g (87%) of a voluminous white solid which was purified by HPLC (EtOAc-Hexane) to give 26.8 mg (6%) of 15 in the first fraction, 272 mg (54%) of 14a as a solid,

mp 142-143.5 °C, in the second fraction, and 35 mg (7%) of impure **14b** in the third fraction.

[659] Example 12

[660] **2-Ethyl-2-((2-Hydroxymethylphenyl)thiomethyl)hexenal (16)**

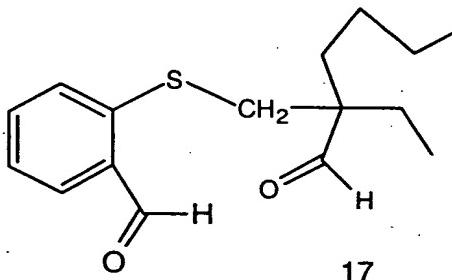


16

[661] A mixture of 5.0 g (0.036 mole) of 2-mercaptobenzyl alcohol, 6.4 g (0.032 mole) of **1**, 3.6 g (0.036 mole) of triethylamine and 25 mL of 2-methoxyethyl ether was held at reflux for 7 h. Additional 1.1 g of mercaptobenzyl alcohol and 0.72 g of triethylamine was added to the reaction mixture and the mixture was held at reflux for additional 16 h. The reaction mixture was cooled and poured into 6N HCl and extracted with methylene chloride. The methylene chloride extract was washed twice with 10% NaOH, dried over MgSO₄ and concentrated in vacuo to give 9.6 g of residue. Purification by HPLC (20% EtOAc-hexane) gave 3.7 g (41%) of **16** as an oil.

[662] Example 13

[663] **2-Ethyl-2-((2-formylphenyl)thiomethyl)hexenal (17)**



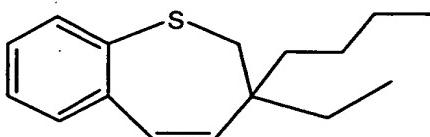
17

[664] A mixture of 3.7 g of **16**, 5.6 g (0.026 mole) of pyridinium chlorochromate, 2 g of Celite and 30 mL of methylene chloride was stirred for 18 h and filtered through a

bed of silica gel. The silica gel was eluted with methylene chloride. The combined methylene chloride eluant was purified by HPLC (20% ETOAc-hexane) to give 2.4 g (66%) of an oil.

[665] Example 14

[666] **3-Butyl-3-ethyl-2,3-dihydrobenzothiepine (18)**

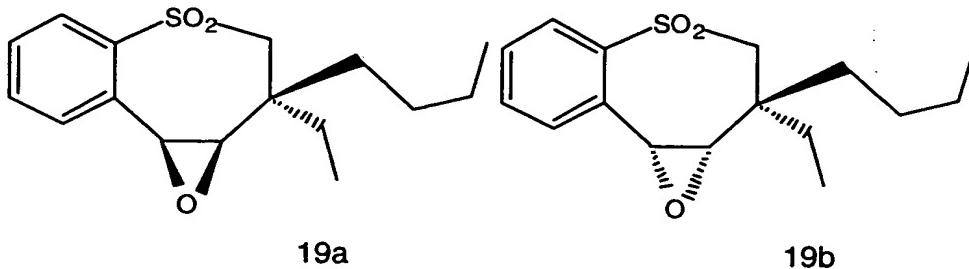


18

[667] A mixture of 2.6 g (0.04 mole) of zinc dust, 7.2 g (0.047 mole) of $TiCl_3$, and 50 mL of DME was held at reflux for 2 h and cooled to room temperature. To this mixture was added 2.4 g (8.6 mmole) of 17 in 20 mL of DME in 10 min. The reaction mixture was stirred at room temperature for 2 h and held at reflux for 1 h then was let standing at room temperature over weekend. The reaction mixture was poured into dilute HCl and was stirred with methylene chloride. The methylene chloride-water mixture was filtered through Celite. The methylene chloride layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 3.0 g of a residue. Purification by HPLC gave 0.41 g (20%) of 18 as an oil in the early fraction.

[668] Example 15

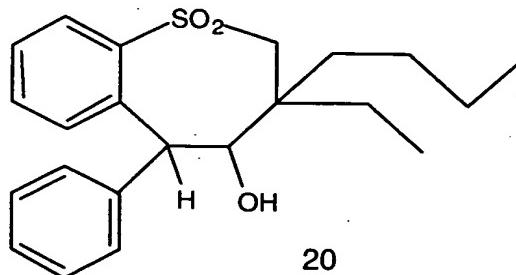
[669] ($1a\alpha,2\alpha,8b\alpha$) **2-Butyl-2-ethyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide (19a)** and ($1a\alpha,2\beta,8b\alpha$) **2-Butyl-2-ethyl-8b-phenyl-1a,2,3,8b-tetrahydro-benzothiepino[4,5-b]oxirene-4,4-dioxide (19b)**



[670] To a solution of 0.4 g of 0.4 g (1.6 mmole) of **18** in 30 mL of methylene chloride was added 2.2 g (3.2 mmole) of 50-60% MCPBA. The reaction mixture was stirred for 2 h and concentrated in vacuo. The residue was dissolved in 30 mL of CHCl₃ and was held at reflux for 18 h under N₂. The reaction mixture was stirred with 100 mL of 10% NaOH and 5 g of sodium sulfite. The methylene chloride layer was washed with brine, dried over MgSO₄ and concentrated in vacuo. The residue was purified by HPLC (20% EtOAc-hexane) to give a third fraction which was further purified by HPLC (10% EtOAc-hexane) to give 0.12 g of syrup in the first fraction. Recrystallization from hexane gave 0.08 g (17%) of **19a**, mp 89.5-105.5 °C. The mother liquor from the first fraction was combined with the second fraction and was further purified by HPLC to give additional **19a** in the first fraction and 60 mg of **19b** in the second fraction. Crystallization from hexane gave 56 mg of a white solid.

[671] Example 16

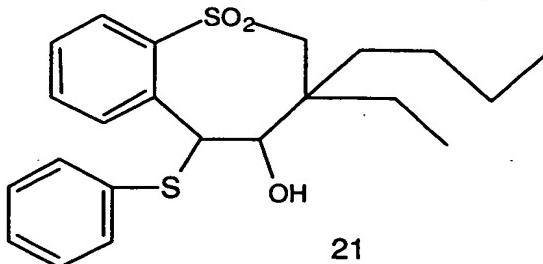
[672] **3-Butyl-3-ethyl-4,5-dihydroxy-5-phenyl-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (20)**



[673] This product was isolated along with **6b** from hydrogenation of a mixture of **8a** and **8b**.

[674] Example 17

[675] 3-Butyl-3-ethyl-4-hydroxy-5-phenylthio-2,3,4,5-tetrahydro-benzothiepine-1,1-dioxide (21)



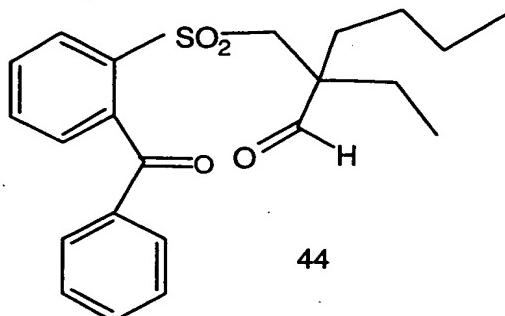
[676] A mixture of 25 mg (0.085 mmole) of **19b**, 0.27 g (2.7 mmole) of thiophenol, 0.37 g (2.7 mmole) of potassium carbonate, and 4 mL of DMF was stirred at room temperature under N₂ for 19 h. The reaction mixture was poured into water and extracted with methylene chloride. The methylene chloride layer was washed successively with 10% NaOH and brine, dried over MgSO₄, and concentrated in vacuo to give 0.19 g of semisolid which contain substantial amounts of diphenyl disulfide. This material was purified by HPLC (5% EtOAc-hexane) to remove diphenyl disulfide in the first fraction. The column was then eluted with 20% EtOAc-hexane to give 17 mg of a first fraction, 4 mg of a second fraction and 11 mg of a third fraction which were three different isomers of **21**, i.e. **21a**, **21b**, and **21c**, respectively, by ¹H NMR and mass spectra.

[677] Example 18

[678] Alternative Synthesis of **6c** and **6d**

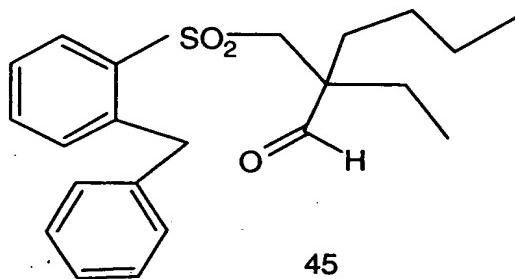
[679] A. Preparation from 2-((2-Benzoylphenylthio)methyl)-2-ethylhexanal (**2**)

[680] Step 1. 2-((2-Benzoylphenylsulfonyl)methyl)-2-ethylhexanal (**44**)



[681] To a solution of 9.0 g (0.025 mole) of compound **2** in 100 ml of methylene chloride was added 14.6 g (0.025 mol) of 50-60% MCPBA portionwise. The reaction mixture was stirred at room temperature for 64 h then was stirred with 200 ml of 1 M potassium carbonate and filtered through Celite. The methylene chloride layer was washed twice with 300 ml of 1 M potassium carbonate, once with 10% sodium hydroxide and once with brine. The insoluble solid formed during washing was removed by filtration through Celite. The methylene chloride solution was dried and concentrated in vacuo to give 9.2 g (95%) of semisolid. A portion (2.6 g) of this solid was purified by HPLC(10% ethyl acetate-hexane) to give 1.9 g of crystals, mp 135-136 °C

[682] Step 2. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (45)



[683] A solution of 50 g (0.13 mole) of crude **44** in 250 ml of methylene chloride was divided in two portions and charged to two Fisher-Porter bottles. To each bottle was charged 125 ml of methanol and 5 g of 10% Pd/C. The bottles were pressurized with 70 psi of hydrogen and the reaction mixture was stirred at room temperature for 7 h before being charged with an additional 5 g of 10% Pd/C. The reaction mixture was again hydrogenated with 70 psi of hydrogen for 7 h. This procedure was repeated one more time but only 1 g of Pd/C was charged to the

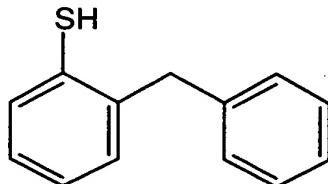
reaction mixture. The combined reaction mixture was filtered and concentrated in vacuo to give 46.8 g of **45** as brown oil.

[684] Step 3. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**6c**), and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**6d**)

[685] To a solution of 27.3 g (73.4 mmole) of **45** in 300 ml of anhydrous THF cooled to 2°C with an ice bath was added 9.7 g (73.4 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred for 20 min, quenched with 300 ml of 10% HCl and extracted with methylene chloride. The methylene chloride layer was dried over magnesium sulfate and concentrated in vacuo to give 24.7 g of yellow oil. Purification by HPLC (ethyl acetate-hexane) yielded 9.4 g of recovered **45** in the first fraction, 5.5 g (20%) of **6c** in the second fraction and 6.5 g (24%) of **6d** in the third fraction.

[686] **B. Preparation from 2-hydroxydiphenylmethane**

[687] **Step 1. 2-mercaptodiphenylmethane (46)**

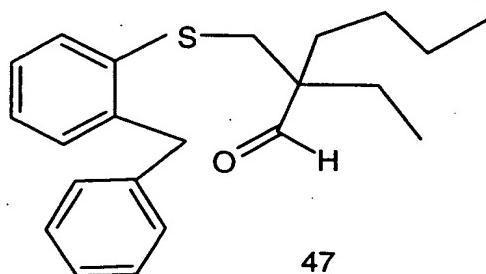


46

[688] To a 500 ml flask was charged 16 g (0.33 mol) of 60% sodium hydride oil dispersion. The sodium hydride was washed twice with 50 ml of hexane. To the reaction flask was charged 100 ml of DMF. To this mixture was added a solution of 55.2 g (0.3 mol) of 2-hydroxydiphenylmethane in 200 ml of DMF in 1 h while temperature was maintained below 30°C by an ice-water bath. After complete addition of the reagent, the mixture was stirred at room temperature for 30 min then cooled with an ice bath. To the reaction mixture was added 49.4 g (0.4 mole) of dimethyl thiocarbamoyl chloride at once. The ice bath was removed and the reaction mixture was stirred at room temperature for 18 h before being poured into

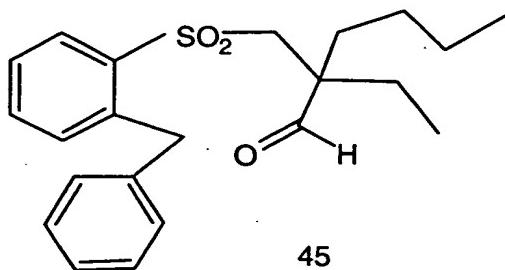
300 ml of water. The organic was extracted into 500 ml of toluene. The toluene layer was washed successively with 10% sodium hydroxide and brine and was concentrated in vacuo to give 78.6 g of a yellow oil which was 95% pure dimethyl *O*-2-benzylphenyl thiocarbamate. This oil was heated at 280-300°C in a kugelrohhr pot under house vacuum for 30 min. The residue was kugelrohr distilled at 1 torr (180-280°C). The distillate (56.3 g) was crystallized from methanol to give 37.3 g (46%) of the rearranged product dimethyl *S*-2-benzylphenyl thiocarbamate as a yellow solid. A mixture of 57 g (0.21 mole) of this yellow solid, 30 g of potassium hydroxide and 150 ml of methanol was stirred overnight then was concentrated in vacuo. The residue was diluted with 200 ml of water and extracted with ether. The aqueous layer was made acidic with concentrate HCl, The oily suspension was extracted into ether. The ether extract was dried over magnesium sulfate and concentrated in vacuo. The residue was crystallized from hexane to give 37.1 g (88%) of 2-mercaptopodiphenylmethane as a yellow solid.

[689] Step 2. 2-((2-Benzylphenylthio)methyl)-2-ethylhexanal (47)

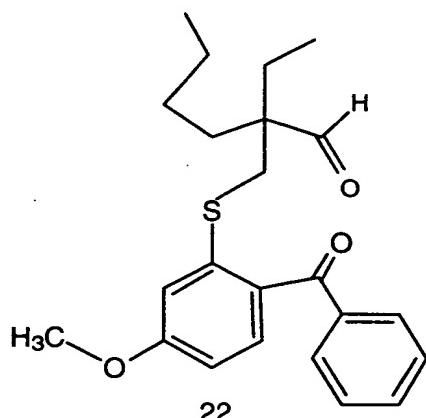


[690] A mixture of 60 g (0.3 mole) of yellow solid from step 1, 70 g (0.3 mole) of compound 1 from preparation 1, 32.4 g (0.32 mole) of triethylamine, 120 ml of 2-methoxyethyl ether was held at reflux for 6 hr and concentrated in vacuo. The residue was triturated with 500 ml of water and 30 ml of concentrate HCl. The organic was extracted into 400 ml of ether. The ether layer was washed successively with brine, 10% sodium hydroxide and brine and was dried over magnesium sulfate and concentrated in vacuo. The residue (98.3 g) was purified by HPLC with 2-5% ethyl acetate-hexane as eluent to give 2-((2-benzylphenylthio)methyl)-2-ethylhexanal 47 as a yellow syrup.

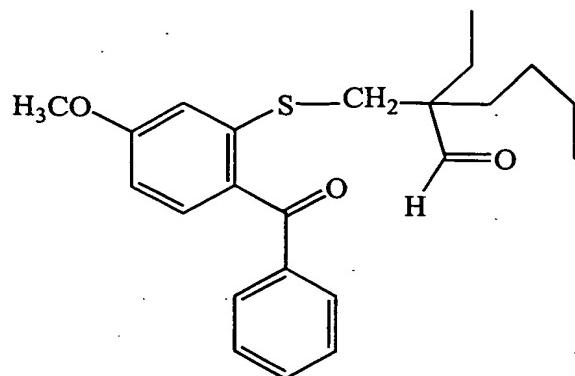
[691] Step 3. 2-((2-Benzylphenylsulfonyl)methyl)-2-ethylhexanal (**45**)



- [692] To a solution of 72.8 g (0.21 mole) of yellow syrup from step 2 in 1 liter of methylene chloride cooled to 10°C was added 132 g of 50-60% MCPBA in 40 min. The reaction mixture was stirred for 2 h. An additional 13 g of 50-60% MCPBA was added to the reaction mixture. The reaction mixture was stirred for 2 h and filtered through Celite. The methylene chloride solution was washed twice with 1 liter of 1 M potassium carbonate then with 1 liter of brine. The methylene chloride layer was dried over magnesium sulfate and concentrated to 76 g of 2-((2-benzylphenylsulfonyl)methyl)-2-ethylhexanal **45** as a syrup.
- [693] Step 4. ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**6c**), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**6d**)
- [694] Reaction of **45** with potassium t-butoxide according to the procedure in step 3 of procedure A gave pure **6c** and **6d** after HPLC.
- [695] Example 19
- [696] ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**25**) and ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**26**)
- [697] Step 1. Preparation of 2-((2-benzoyl-4-methoxy phenylthio)methyl)-2-ethylhexanal (**22**)



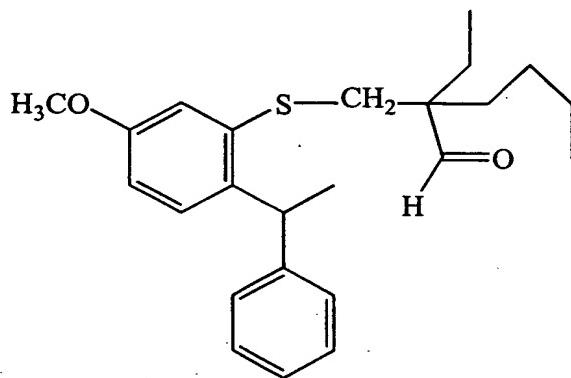
- [698] 2-Hydroxy-4-methoxybenzophenone was converted to the dimethyl *O*-2-benzoylphenyl thiocarbamate by methods previously described in example 18. The product can be isolated by recrystallization from ethanol. Using this improved isolation procedure no chromatography was needed. The thermal rearrangement was performed by reacting the thiocarbamate(5 g) in diphenyl ether at 260°C as previously described. The improved isolation procedure which avoided a chromatography step was described below.
- [699] The crude pyrolysis product was then heated at 65°C in 100 ml of methanol and 100 ml of THF in the presence of 3.5 g of KOH for 4 h. After removing THF and methanol by rotary evaporation the solution was extracted with 5 % NaOH and ether. The base layer was acidified and extracted with ether to obtain a 2.9 g of crude thiophenol product. The product was further purified by titrating the desired mercaptan into base with limited KOH. After acidification and extraction with ether pure 2-mercaptop-4-methoxybenzophenone (2.3 g) was isolated.
- [700] 2-mercaptop-4-methoxybenzophenone can readily be converted to the 2-((2-benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (22) by reaction with 2-ethyl-2-(mesyloxymethyl)hexanal (1) as previously described.
- [701] Step 2. 2-((2-Benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23)



23

[702] Substrate 22 was readily oxidized to 2-((2-benzoyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (23) as described in example 18.

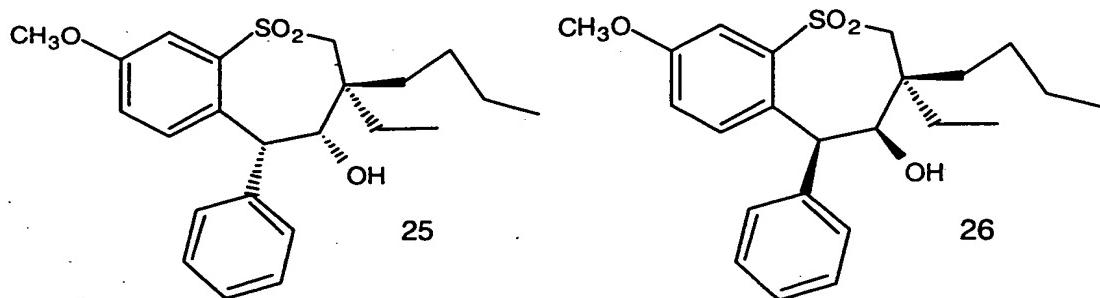
[703] Step 3. 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (24)



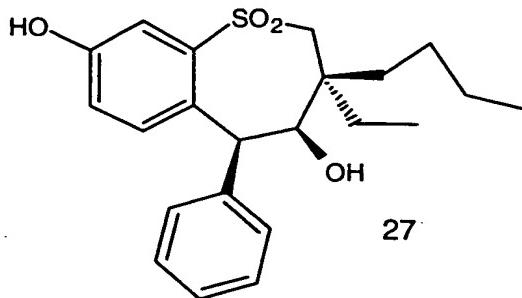
24

[704] Sulfone 23 was then reduced to 2-((2-benzyl-5-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (24) as described in example 18.

[705] Step 4. ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (25) and ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-8-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (26)



- [706] A 3-neck flask equipped with a powder addition funnel, thermocouple and nitrogen bubbler was charged with 19.8 g (0.05 mole) of sulfone **24** in 100 ml dry THF. The reaction was cooled to -1.6°C internal temperature by means of ice/salt bath. Slowly add 5.61 g (0.05 mole) of potassium t-butoxide by means of the powder addition funnel. The resulting light yellow solution was maintained at -1.6 °C. After 30 min reaction 400 ml of cold ether was added and this solution was extracted with cold 10 % HCl. The acid layer was extracted with 300 ml of methylene chloride. The organic layers were combined and dried over magnesium sulfate and after filtration stripped to dryness to obtain 19.9 g of product. ¹H nmr and glpc indicated a 96% conversion to a 50/50 mixture of **25** and **26**. The only other observable compound was 4% starting sulfone **24**.
- [707] The product was then dissolved in 250 ml of 90/10 hexane/ethyl acetate by warming to 50 °C. The solution was allowed to cool to room temperature and in this way pure **26** can be isolated. The crystallization can be enhanced by addition of a seed crystal of **26**. After 2 crystallizations the mother liquor which was now 85.4% **25** and has a dry weight of 8.7 g. This material was dissolved in 100 ml of 90/10 hexane/ethyl acetate and 10 ml of pure ethyl acetate at 40°C. Pure **25** can be isolated by seeding this solution with a seed crystal of **25** after storing it overnight at 0°C.
- [708] Example 20
- [709] **(3α,4α,5α)-3-Butyl-3-ethyl-4,8-dihydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (27)**



[710] In a 25 ml round bottomed flask, 1 g of **26**(2.5 mmoles) and 10 ml methylene chloride were cooled to - 78°C with stirring. Next 0.7 ml of boron tribromide(7.5 mmole) was added via syringe. The reaction was allowed to slowly warm to room temperature and stirred for 6 h. The reaction was then diluted with 50 ml methylene chloride and washed with saturated NaCl and then water. The organic layer was dried over magnesium sulfate. The product (0.88g) **27** was characterized by NMR and mass spectra.

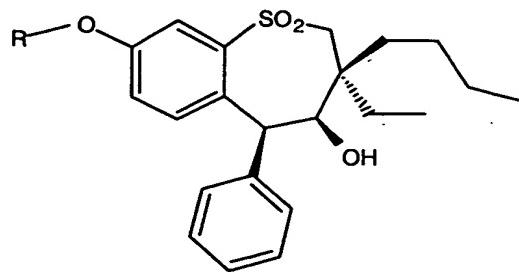
[711] Example 21

[712] **General Alkylation of phenol 27**

[713] A 25 ml flask was charged with 0.15 g of **27**(0.38 mmole), 5 ml anhydrous DMF, 54 mg of potassium carbonate(0.38 mmole) and 140 mg ethyl iodide (0.9 mmole). The reaction was stirred at room temperature overnight. The reaction was diluted with 50 ml ethyl ether and washed with water (25 ml) then 5% NaOH (20 ml) and then sat. NaCl. After stripping off the solvent the ethoxylated product **28** was obtained in high yield. The product was characterized by NMR and mass spectra.

[714] This same procedure was used to prepare products listed in table 1 from the corresponding iodides or bromides. For higher boiling alkyl iodides and bromides only one equivalent of the alkyl halide was used.

Table 2



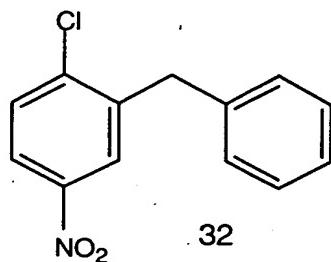
Formula for Table 2

Compound No.	R
27	H
26	Me
28	Et
29	Hexyl
30	Ac
31	(CH ₂) ₆ -N-pthalimide

[715] Example 22

[716] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (37) and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)

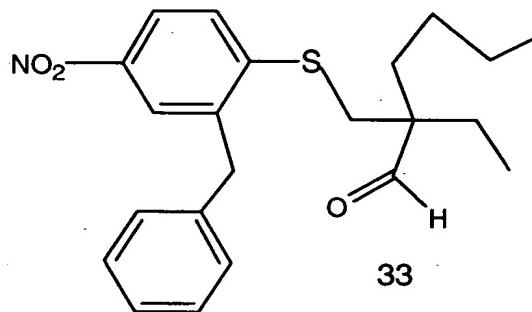
[717] Step 1. Preparation of 2-chloro-5-nitrodiphenylmethane (32)



[718] Procedure adapted from reference :Synthesis -Stuttgart 9, 770-772 (1986) Olah G. et al.

[719] Under nitrogen, a 3 neck flask was charged with 45 g (0.172 mole) of 2-chloro-5-nitrobenzophenone in 345 ml methylene chloride and the solution was cooled to ice/water temperature. By means of an additional funnel, 150 g (0.172 mole) of trifluoromethane sulfonic acid in 345 ml methylene chloride was added slowly. Next 30 g of triethylsilane (0.172 mole) in 345 ml methylene chloride was added dropwise to the chilled solution. Both addition steps (trifluoromethane sulfonic acid and triethylsilane) were repeated. After the additions were completed the reaction was allowed to slowly warm up to room temperature and stirred for 12 h under nitrogen. The reaction mixture was then poured into a chilled stirred solution of 1600 ml of saturated sodium bicarbonate. Gas evolution occurred. Poured into a 4 liter separatory funnel and separated layers. The methylene chloride layer was isolated and combined with two 500 ml methylene chloride extractions of the aqueous layer. The methylene chloride solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from hexane to give 39 g product. Structure 32 was confirmed by mass spectra and proton and carbon NMR.

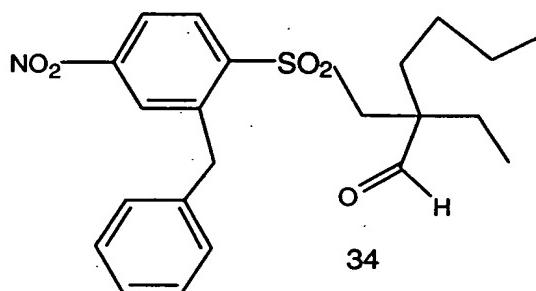
[720] **Step 2. Preparation of 2-((2-benzyl-4-nitrophenylthio)methyl)-2-ethylhexanal (33)**



[721] The 2-chloro-5-nitrodiphenylmethane product 32 (40 g, 0.156 mole) from above was placed in a 2 liter 2 neck flask with water condenser. Next 150 ml DMSO and 7.18 g (0.156 mole) of lithium sulfide was added and the solution was stirred at 75°C for 12 h. The reaction was cooled to room temperature and then 51.7 g of mesylate IV was added in 90 ml DMSO. The reaction mixture was heated to 80°C under nitrogen. After 12 h monitored by TLC and added more mesylate if necessary. Continued the reaction until the reaction was completed. Next the

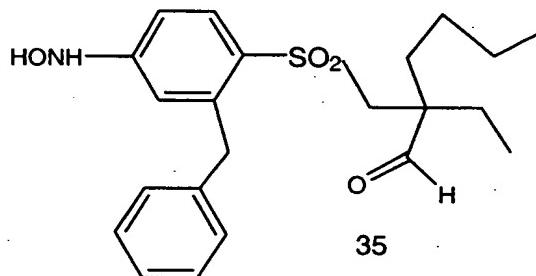
reaction mixture was slowly poured into a 1900 ml of 5% acetic aqueous solution with stirring, extracted with 4 X 700 ml of ether, and dried over MgSO₄. After removal of ether, 82.7 g of product was isolated. The material can be further purified by silica gel chromatography using 95% hexane and 5 % ethyl acetate. If pure mysylate was used in this step there was no need for further purification. The product 33 was characterized by mass spectra and NMR.

[722] Step 3. Oxidation of the nitro product 33 to the sulfone 2-((2-benzyl-4-nitrophenoxy)sulfonyl)methyl)-2-ethylhexanal (34)



[723] The procedure used to oxidize the sulfide 33 to the sulfone 34 has been previously described.

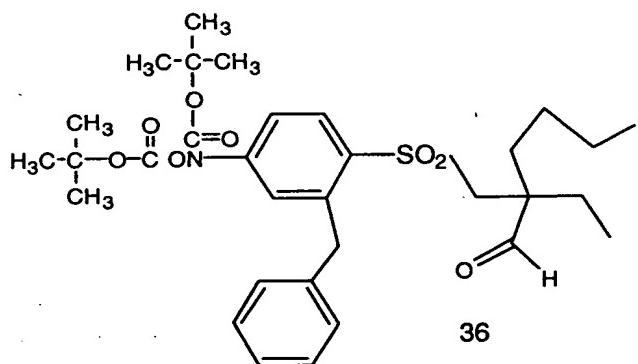
[724] Step 4. Reduction of 34 to 2-((2-benzyl-4-hydroxyaminophenoxy)sulfonyl)methyl)-2-ethylhexanal (35)



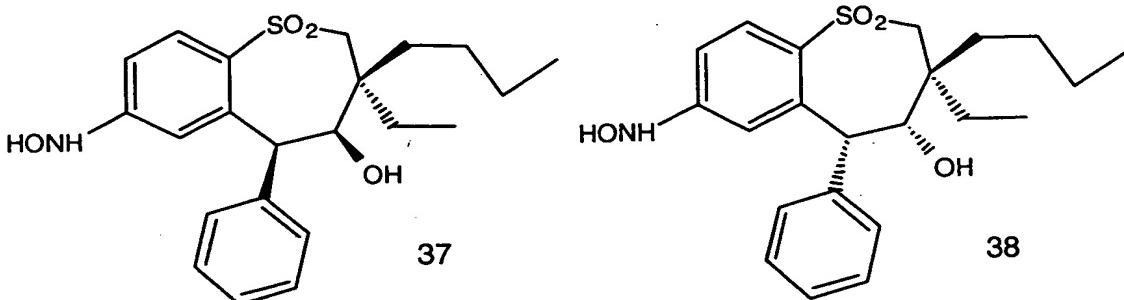
[725] A 15 g sample of 34 was dissolved in 230 ml of ethanol and placed in a 500 ml rb flask under nitrogen. Next 1.5 g of 10 wt.% Pd/C was added and hydrogen gas was bubbled through the solution at room temperature until the nitro substrate 34 was consumed. The reaction could be readily monitored by silica gel TLC using 80/20 hexane/EtOAc. Product 35 was isolated by filtering off the Pd/C and then

stripping off the EtOH solvent. The product was characterized by NMR and mass spectra.

- [726] Step 5. Preparation of the 2-((2-benzyl-4-N,O-di-(t-butoxy-carbonyl)hydroxyaminophenylsulfonyl)methyl)-2-ethylhexanal (36).



- [727] A 13.35 g sample of 35 (0.0344 mole) in 40 ml of dry THF was stirred in a 250 ml round bottomed flask. Next added 7.52 g (0.0344 mole) of di-t-butyl dicarbonate in 7 ml THF. Heated at 60°C overnight. Stripped off THF and redissolved in methylene chloride. Extracted with 1 % HCl; and then 5% sodium bicarbonate.
- [728] The product was further purified by column chromatography using 90/10 hexane/ethyl acetate and then 70/30 hexane/ethyl acetate. The product 36 was obtained (4.12 g) which appeared to be mainly the di-(t-butoxycarbonyl) derivatives by proton NMR.
- [729] Step 6. (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (37) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-7-hydroxyamino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (38)



[730] A 250ml 3-neck round bottomed flask was charged with 4 g of **36** (6.8 mmoles), and 100 ml of anhydrous THF and cooled to -78°C under a nitrogen atmosphere. Slowly add 2.29 g potassium tert-butoxide(20.4 mmoles) with stirring and maintaining a -78°C reaction temperature. After 1 h at -78°C the addition of base was completed and the temperature was brought to -10°C by means of a ice/salt bath. After 3 h at -10 °C, only trace **36** remained by TLC. Next add 35 ml of deionized water to the reaction mixture at -10°C and stirred for 5 min. Stripped off most of the THF and added to separatory funnel and extracted with ether until all of the organic was removed from the water phase. The combined ether phases were washed with saturated NaCl and then dried over sodium sulfate. The only products by TLC and NMR were the two BOC protected isomers of **37** and **38**. The isomers were separated by silica gel chromatography using 85% hexane and 15 % ethyl acetate; **BOC-37** (0.71 g) and **BOC- 38** (0.78 g).

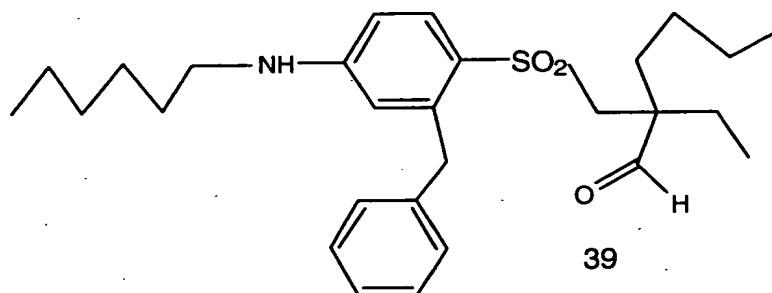
[731] Next the BOC protecting group was removed by reacting 0.87 g of **BOC-38** (1.78 mmoles) with 8.7 ml of 4 M HCl (34.8 mmoles)in dioxane for 30 min. Next added 4.74 g of sodium acetate (34.8 mmoles) to the reaction mixture and 16.5 ml ether and stirred until clear. After transferring to a separatory funnel extracted with ether and water and then dried the ether layer with sodium sulfate. After removing the ether, 0.665 g of **38** was isolated. Isomer **37** could be obtained in a similar procedure.

[732] Example 23

[733] (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**40**) and (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-7-(n-

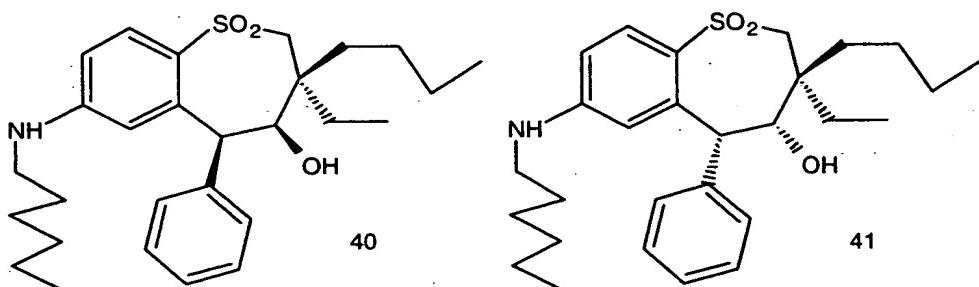
**hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(41)**

- [734] **Step 1.** 2-((2-Benzyl-4-(n-hexylamino)phenylsulfonyl)methyl)-2-ethylhexanal (39)



[735] In a Fischer porter bottle weighed out 0.5 g of 34 (1.2 mmoles) and dissolved in 3.8 ml of ethanol under nitrogen. Next added 0.1 g of Pd/C and 3.8 ml of hexanal. Seal and pressure to 50 psi of hydrogen gas. Stirred for 48 h. After filtering off the catalyst and removing the solvent by rotary evaporation 39 was isolated by column chromatography (0.16 g) using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. The product was characterized by NMR and mass spectra.

- [736] **Step 2.** ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (40) and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-7-(n-hexylamino)-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (41)



- [737] A 2-neck, 25 ml round bottomed flask with stir bar was charged with 0.158 g 39 (0.335 mmole) and 5 ml anhydrous THF under nitrogen. Cool to -10°C by means

of a salt/water bath. Slowly add 0.113 g of potassium tert butoxide (0.335 mmole). After 15 min at -10°C all of the starting material was consumed by TLC and only the two isomers **40** and **41** were observed. Next added 5 ml of chilled 10% HCl and stirred at -10°C for 5 min. Transferred to a separatory funnel and extract with ether. Dried over sodium sulfate. Proton NMR of the dried product (0.143 g) indicated only the presence of the two isomers **40** and **41**. The two isomers were separated by silica gel chromatography using 90/10 hexane ethyl acetate and gradually increasing the mobile phase to 70/30 hexane/ethyl acetate. **40** (53.2 mg); **41**(58.9 mg).

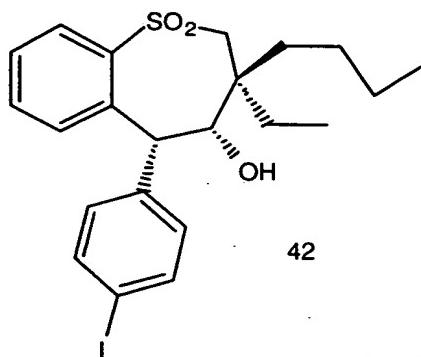
[738] Example 24

[739] **Quaternization of amine substrates **40** and **41****

[740] Amine products such as **40** and **41** can be readily alkylated to quaternary salts by reaction with alkyl halides. For example **40** in DMF with 5 equivalents of methyl iodide in the presence of 2,6 dimethyl lutidine produces the dimethylhexylamino quaternary salt.

[741] Example 25

[742] **(3 α ,4 β ,5 β) 3-Butyl-3-ethyl-4-hydroxy-5-(4-iodophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (42)**

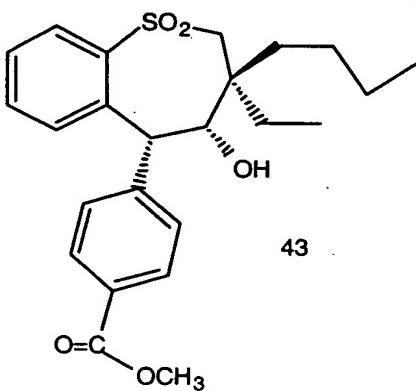


[743] In a 25 ml round bottomed flask 0.5 g (1.3 mmole) of **6d** , 0.67 g of mercuric triflate were dissolved in 20 ml of dry methylene chloride with stirring. Next 0.34 g of Iodine was added and the solution was stirred at room temperature for 30 h.

The reaction was then diluted with 50 ml methylene chloride and washed with 10 ml of 1 M sodium thiosulfate; 10 ml of saturated KI ; and dried over sodium sulfate. See Tetrahedron, Vol.50, No. 17, pp 5139-5146 (1994) Bachki, F. Et al. Mass spectrum indicated a mixture of **6d** , mono iodide **42** and a diiodide adduct. The mixture was separated by column chromatography and **42** was characterized by NMR and mass spectra.

[744] Example 26

- [745] ($3\alpha,4\beta,5\beta$) **3-Butyl-5-(4-carbomethoxyphenyl)-3-ethyl-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (43)**



- [746] A 0.1 g sample of **42** (0.212 mmole), 2.5 ml dry methanol, 38 μ l triethylamine (0.275 mmole) , 0.3 ml toluene and 37 mg of palladium chloride (0.21 mmole) was charged to a glass lined mini reactor at 300 psi carbon monoxide. The reaction was heated at 100°C overnight. The catalyst was filtered and a high yield of product was isolated.

- [747] The product was characterized by NMR and mass spectra.

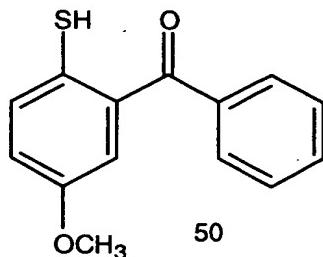
- [748] Note the ester functionalized product **43** can be converted to the free acid by hydrolysis.

[749] Example 27

- [750] ($3\alpha,4\alpha,5\alpha$) **3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (48)**, and ($3\alpha,4\beta,5\beta$) **3-Butyl-3-ethyl-4-**

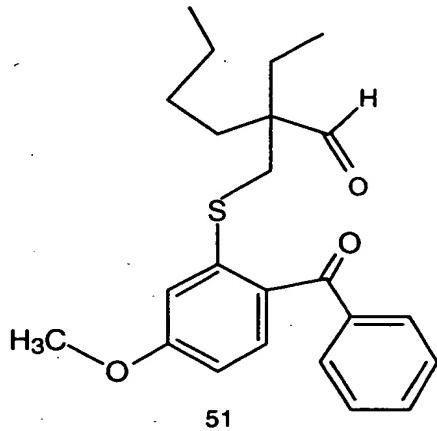
**hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide
(49)**

[751] **Step 1. 2-Mercapto-5-methoxybenzophenone (50)**



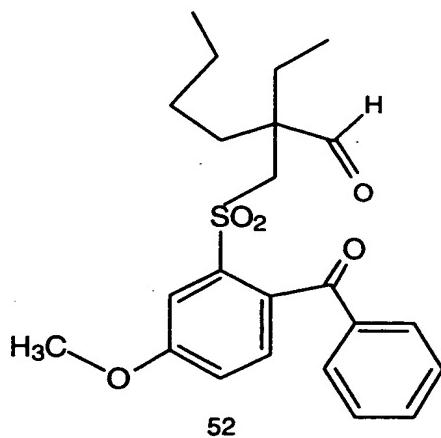
[752] Reaction of 66.2 g of 4-methoxythiophenol with 360 ml of 2.5 N n-butyllithium, 105 g of tetramethylethylenediamine and 66.7 g of benzonitrile in 600 ml cyclohexane according to the procedure in WO 93/16055 gave 73.2 g of brown oil which was kugelrohr distilled to remove 4-methoxythiophenol and gave 43.86 g of crude **50** in the pot residue.

[753] **Step 2. 2-((2-Benzoyl-4-methoxyphenylthio)methyl)-2-ethylhexanal (51)**

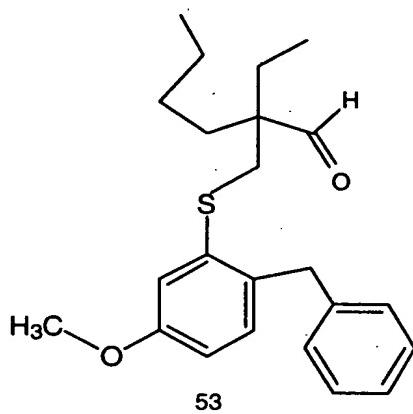


[754] Reaction of 10 g (0.04 mole) of crude **50** with 4.8 g (0.02 mole) of mesylate **1** and 3.2 ml (0.23 mole) of triethylamine in 50 ml of diglyme according to the procedure for the preparation of **2** gave 10.5 g of crude product which was purified by HPLC (5% ethyl acetate-hexane) to give 1.7 g (22%) of **51**.

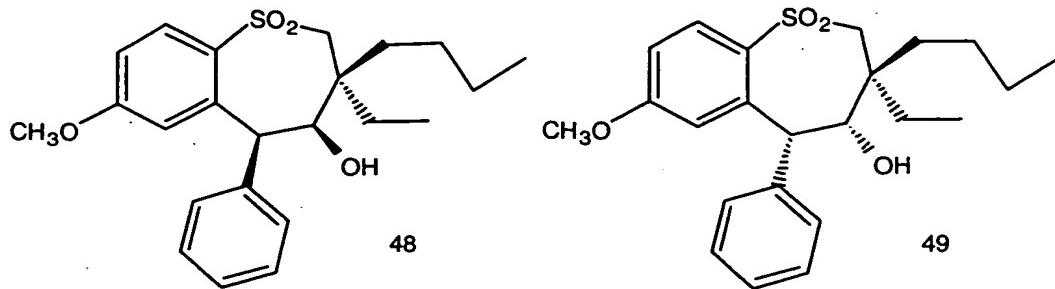
[755] **Step 3. 2-((2-Benzoyl-4-methoxyphenylsulfanyl)methyl)-2-ethylhexanal (52)**



- [756] A solution of 1.2 g (3.1 mmoles) of **51** in 25 ml of methylene chloride was reacted with 2.0 g (6.2 mmoles) of 50-60% MCPBA according to the procedure of step 2 of procedure A in example 18 gave 1.16 g (90%) of **52** as a yellow oil.
- [757] **Step 4.** 2-((2-Benzyl-4-methoxyphenylsulfonyl)methyl)-2-ethylhexanal (**53**)



- [758] Hydrogenation of 1.1 g of **52** according to the procedure of step 3 of procedure A of example 18 gave **53** as a yellow oil (1.1 g).
- [759] **Step 5.** ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**48**), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (**49**)

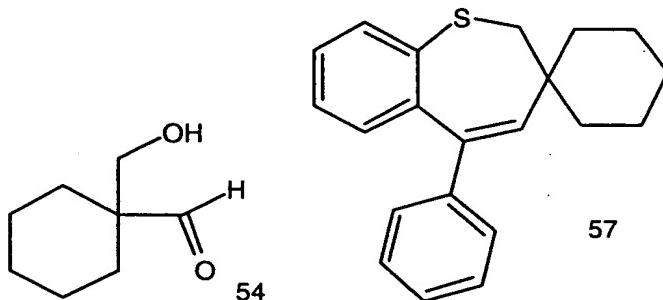


[760] A solution of 1.1 g of **53**, 0.36 g of potassium t-butoxide and 25 ml of anhydrous THF was held at reflux for 2 h and worked up as in step 4 of procedure A of example 18 to give 1.07 g of a crude product which was purified by HPLC to give 40 mg (4%) of **48** as crystals, mp 153-154°C and 90 mg (8%) of **49** as solid, mp 136-140°C.

[761] Example 28

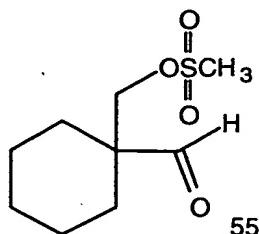
[762] **5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)**

[763] **Step 1. 1-(Hydroxymethyl)-cyclohexanecarboxaldehyde (54)**



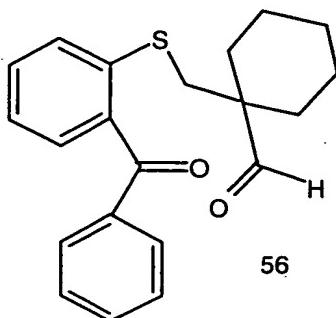
[764] To a cold (0 °C) mixture of 100 g (0.891 mole) of cyclohexanecarboxaldehyde, 76.5 g of 37% of formaldehyde in 225 ml of methanol was added dropwise 90 ml of 1 N Sodium hydroxide in 1 h. The reaction mixture was stirred at room temperature over 48 then was evaporated to remove methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 75 g (59.7%) of thick oil. Proton NMR and mass spectra were consistent with the product.

[765] Step 2. 1-(mesyloxymethyl)cyclohexanecarboxaldehyde (55)



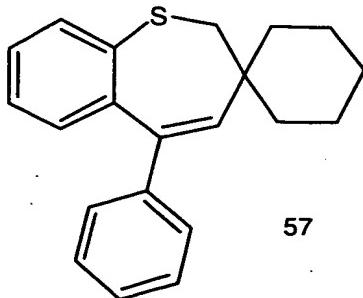
[766] To a cold (0°C) mixture of alcohol **54** (75 g, 0.54 mole) and 65.29 g (0.57 mole) of methanesulfonyl chloride in 80 ml of methylene chloride was added a solution of pyridine (47.96 g, 0.57 mole) in 40 ml of methylene chloride. The reaction mixture was stirred at room temperature for 18 h then quenched with water, acidified with conc. HCl and extracted with methylene chloride. The organic layer was washed with water, brine, and dried over sodium sulfate and concentrated under vacuum to give 91.63 g (77.8%) of thick oil. Proton NMR and mass spectra were consistent with the product.

[767] Step 3. 1-((2-Benzoylphenylthio)methyl)cyclohexanecarboxaldehyde (56)



[768] A mixture of 69 g (0.303 mole) of 2-mercaptopbenzophenone, 82 g (0.303 mole) of mesylate **55**, 32 g of triethylamine, and 150 ml of diglyme was stirred and held at reflux for 24 h. The mixture was cooled, poured into dil. HCl and extracted with methylene chloride. The organic layer was washed with 10% NaOH, water, brine, and dried over sodium sulfate and concentrated under vacuum to remove excess diglyme. This was purified by silica gel flush column (5% EtOAc: Hexane) and gave 18.6 g (75.9%) of yellow oil. Proton NMR and mass spectra were consistent with the product.

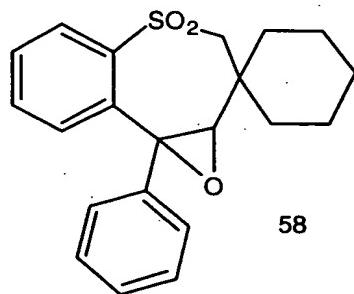
[769] Step 4. 5-Phenyl-2,3-dihydrospirobenzothiepine-3,1'-cyclohexane (57)



[770] To a mixture of 6.19 g of zinc dust and 100 ml of dry DME was added TiCl₃(16.8 g, 0.108 mole). The reaction mixture was heated to reflux for 2 h. A solution of compound 56 (8.3 g, 0.023 mole) in 50 ml of DME was added dropwise to the reaction mixture in 1 h and the mixture was held at reflux for 18 h. The mixture was cooled, poured into water and extracted with ether. The organic layer was washed with water, brine, and dried over sodium sulfate, filtered through celite and concentrated under vacuum. The residue was purified by HPLC (10% EtOAc: Hexane) to give 4.6 g (64%) of white solid, mp 90-91 °C. Proton and carbon NMR and mass spectra were consistent with the product.

[771] Example 29

[772] **8b-Phenyl-1a,2,3,8b-tetrahydrospiro(benzothiepino[4,5-b]oxirene-2,1'-cyclohexane)-4,4-dioxide (58)**

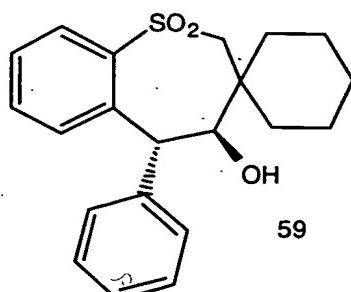


[773] To a solution of 57 (4.6 g, 15 mmole) in 50 ml chloroform under nitrogen was added 55% MCPBA (16.5 g, 52.6 mmole) portionwise with spatula. The reaction was held at reflux for 18 h and washed with 10% NaOH(3X), water, brine, and dried over sodium sulfate and concentrated under vacuum to give 5 g of crude

product. This was recrystallized from Hexane/EtOAc to give 4.31 g (81%) of yellow solid, mp 154-155 °C. Proton and carbon NMR and mass spectra were consistent with the product.

[774] Example 30

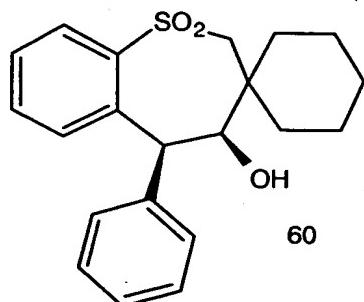
- [775] **trans-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (59)**



- [776] A mixture of 0.5 g (1.4 mmoles) of **58**, 20 ml of ethanol, 10 ml of methylene chloride and 0.4 g of 10% Pd/C catalyst was hydrogenated with 70 psi hydrogen for 3 h at room temperature. The crude reaction slurry was filtered through Celite and evaporated to dryness. The residue was purified by HPLC (10% EtOAc-Hexane, 25% EtOAc-Hexane). The first fraction was 300 mg (60%) as a white solid, mp 99-100 °C. Proton NMR showed this was a trans isomer. The second fraction gave 200 mg of solid which was impure cis isomer.

[777] Example 31

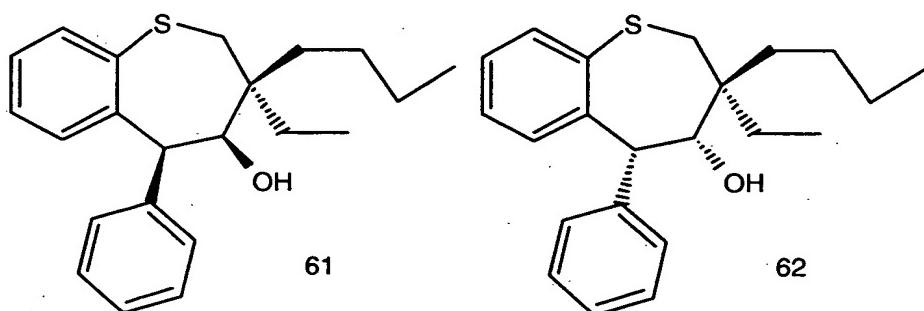
- [778] **cis-4-Hydroxy-5-phenyl-2,3,4,5-tetrahydro spiro(benzothiepine-3,1'-cyclohexane)-1,1-dioxide (60)**



[779] To a solution of 0.2 g (0.56 mmole) of **59** in 20 ml of CH₂Cl₂, was added 8 g of 50% NaOH and one drop of Aliquat-336 (methyltricaprylylammonium chloride) phase transfer catalyst. The reaction mixture was stirred for 10 h at room temperature. Twenty g of ice was added to the mixture and the mixture was extracted with CH₂Cl₂ (3x10 ml) washed with water, brine and dried over MgSO₄ and concentrated in vacuo to recover 0.15 g of crude product. This was recrystallized from Hexane/EtOAc to give 125 mg of white crystal, mp 209-210°C. Proton and carbon NMR and mass spectra were consistent with the product.

[780] Example 32

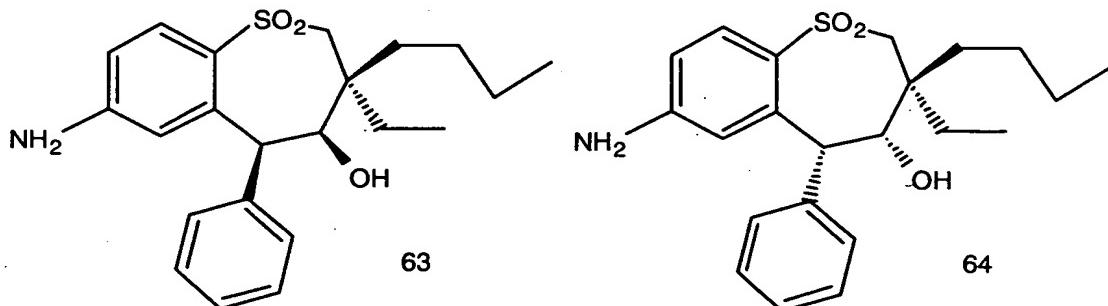
[781] (*3 α ,4 α ,5 α*) **3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (61)**, and (*3 α ,4 β ,5 β*) **3-Butyl-3-ethyl-4-hydroxy-5-phenyl-2,3,4,5-tetrahydrobenzothiepine (62)**



[782] To a solution of 0.5 g (1.47 mmole) of compound **47** in 5 ml of anhydrous THF was added 0.17 g (1.47 mmole) of 95% potassium t-butoxide. The reaction mixture was stirred at room temperature for 18 h and quenched with 10 ml of 10% HCl. The organic was extracted into methylene chloride. The methylene chloride extract was dried over magnesium sulfate and concentrated in vacuo. The residue was purified by HPLC (2% EtOAc-hexane) to give 47 mg of **61** in the second fraction and 38 mg of **62** in the third fraction. Proton NMR and mass spectra were consistent with the assigned structures.

[783] Example 33

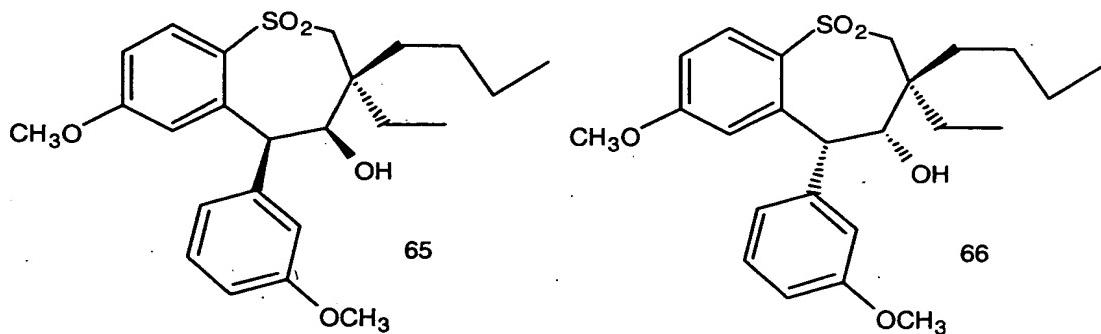
[784] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (63) and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-7-amino-5-phenyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide(64)



[785] An autoclave was charged with 200 mg of 37 in 40 cc ethanol and .02 g 10 % Pd/C. After purging with nitrogen the clave was charged with 100 psi hydrogen and heated to 55°C. The reaction was monitored by TLC and mass spec and allowed to proceed until all of 37 was consumed. After the reaction was complete the catalyst was filtered and the solvent was removed in vacuo and the only observable product was amine 63. This same procedure was used to produce 64 from 38.

[786] Example 34

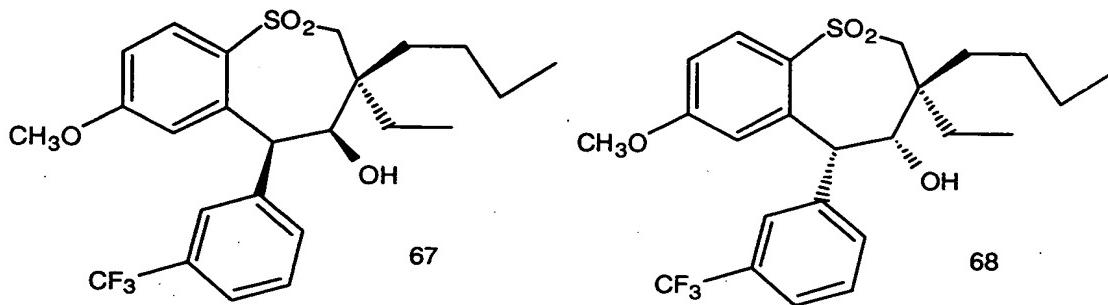
[787] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (65), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (66).



[788] Alkylation of e-methoxyphenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-methoxybenzyl)phenol in 35% yield. This material was converted to compound 65, mp 138.5-141.5 °C, and compound 66, mp 115.5-117.5 °C, by the procedure similar to that in Example 18 method B.

[789] Example 35

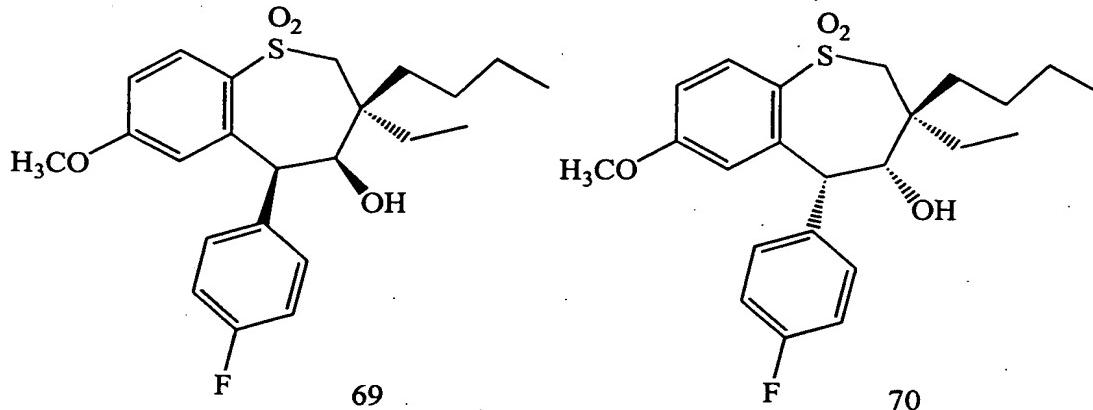
- [790] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (67), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-7-methoxy-5-(3'-trifluoromethyl)phenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (68).



- [791] Alkylation of 4-methoxyphenol with 3-(trifluoromethyl)benzyl chloride according to the procedure described in J. Chem. Soc. 2431 (1958) gave 4-methoxy-2-(3'-trifluoromethyl)benzylphenol. This material was converted to compound 67, mp 226.5-228 °C, and compound 68, mp 188-190°C, by the procedure similar to that in Example 18 method B.

[792] Example 36

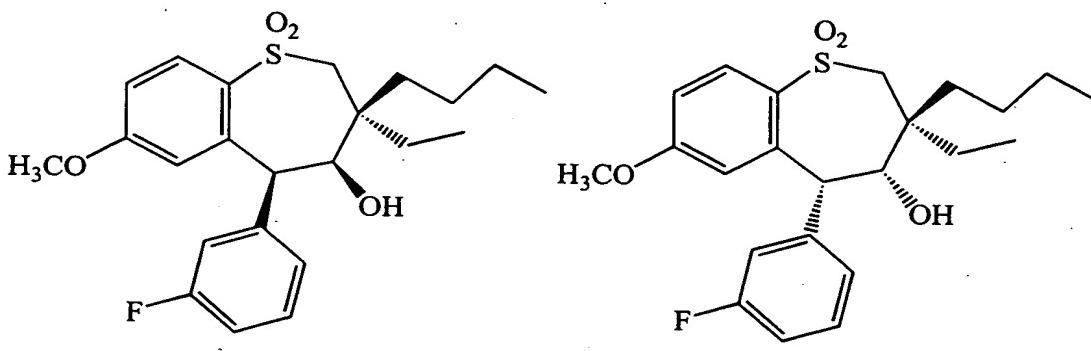
- [793] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (69), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (70).



[794] Alkylation of 4-methoxyphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(4'-fluorobenzyl)phenol. This material was converted to compound 69 and compound 70 by the procedure similar to that in Example 18 method B.

[795] Example 37

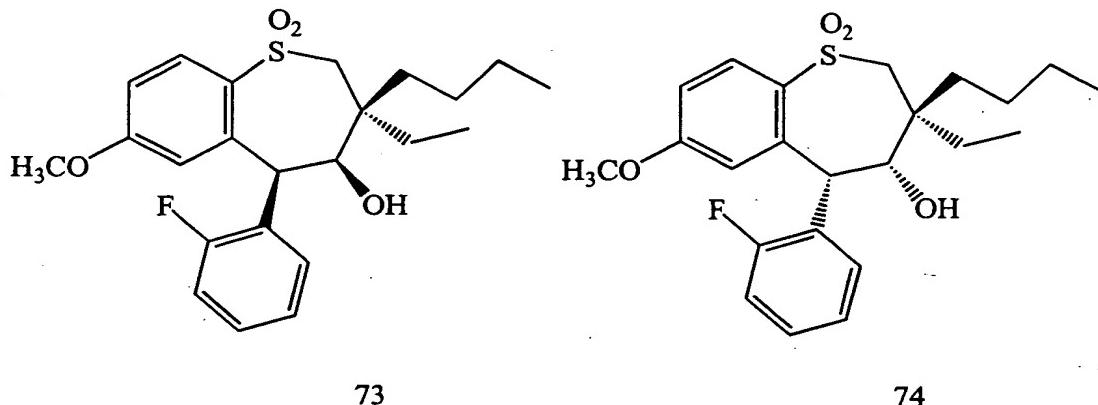
[796] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (71), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(3'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (72).



[797] Alkylation of 4-methoxyphenol with 3-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methoxy-2-(3'-fluorobenzyl)phenol. This material was converted to compound 71 and compound 72 by the procedure similar to that in Example 18 method B.

[798] Example 38

[799] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (73), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(2'-fluorophenyl)-4-hydroxy-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (74).



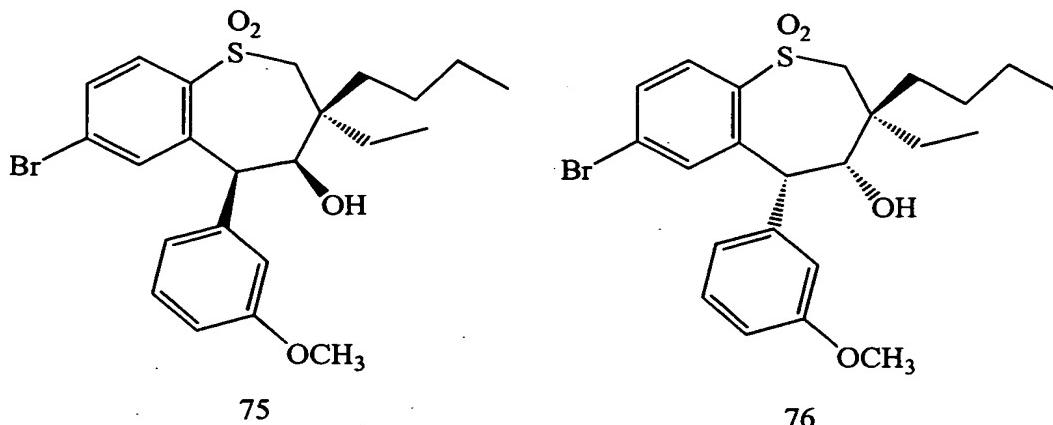
73

74

[800] Alkylation of 4-methoxyphenol with 2-fluorobenzyl chloride according to the procedure described in J. Chem. Soc., 2431 (1958) gave 4-methoxy-2-(2'-fluorobenzyl)phenol. This material was converted to compound 73 and compound 74 by the procedure similar to that in Example 18 method B.

[801] Example 39

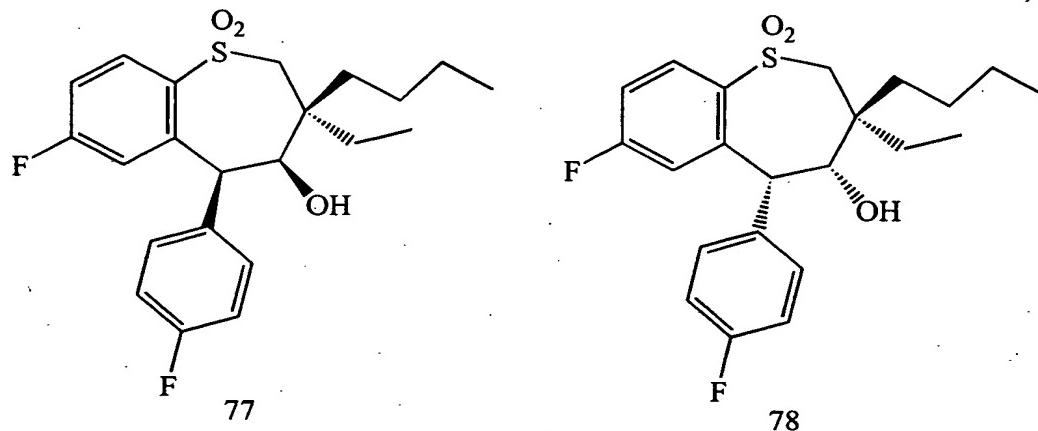
[802] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (75), and ($3\alpha,4\beta,5\beta$) 3-Butyl-7-bromo-3-ethyl-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (76).



- [803] Alkylation of 4-bromophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-bromo-2-(3'-methoxybenzyl)phenol. This material was converted to compound 75, mp 97-101.5 °C, and compound 76, mp 102-106 °C, by the procedure similar to that in Example 18 method B.

[804] Example 40

- [805] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (77), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-7-fluoro-5-(4'-fluorophenyl)-4-hydroxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (78).

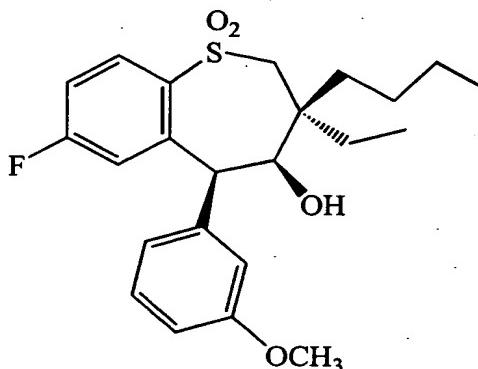


- [806] Alkylation of 4-fluorophenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(4'-fluorobenzyl)phenol. This material was converted to compound 77, mp 228-230

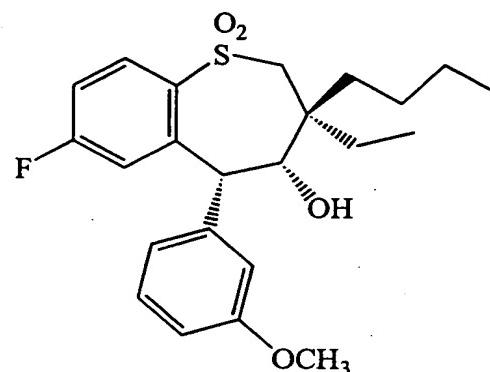
°C, and compound 78, mp 134.5-139 °C, by the procedure similar to that in Example 18 method B.

[807] Example 41

[808] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (79), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-7-fluoro-4-hydroxy-5-(3'-methoxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (80).



79

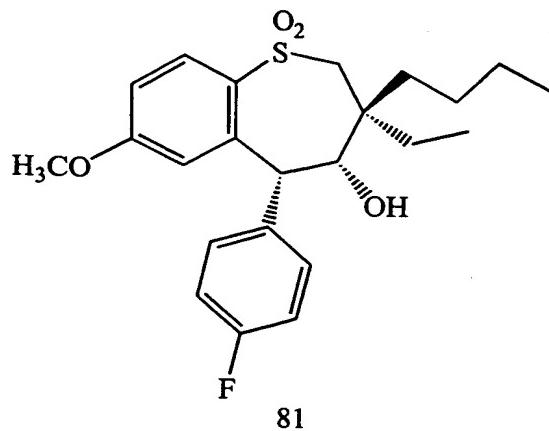


80

[809] Alkylation of 4-fluorophenol with 3-methoxybenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-fluoro-2-(3'-methoxybenzyl)phenol. This material was converted to compound 79, as a solid and compound 80, mp 153-155 °C, by the procedure similar to that in Example 18 method B.

[810] Example 42

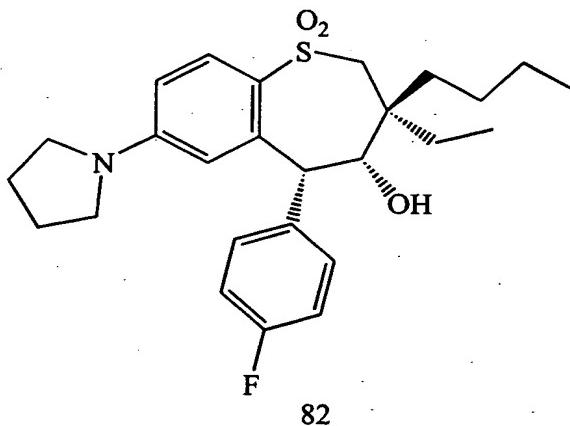
[811] ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (81).



[812] A mixture of 0.68 (1.66 mmol) of compound 77, 0.2 g (5 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at room temperature for 16 days. The reaction mixture was dilute with ether and washed with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was purified by HPLC (20% ethyl acetate in hexanes). The first fraction was impure ($3\alpha,4\alpha,5\alpha$) 3-butyl-3-ethyl-4-hydroxy-7-methylthio-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide. The second fraction was compound 81, mp 185-186.5 °C.

[813] Example 43

[814] ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-pyrrolidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (82).

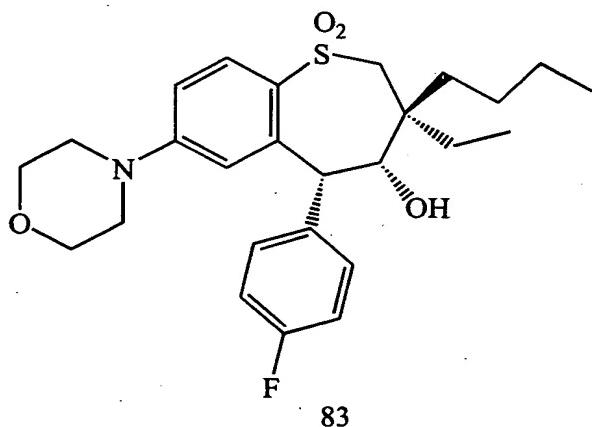


[815] A mixture of 0.53 g (1.30 mmol) of compound 78 and 5 ml of pyrrolidine was held at reflux for 1 h. The reaction mixture was diluted with ether and washed

with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was crystallized from ether-hexanes to give compound 82, mp 174.5-177 °C.

[816] Example 44

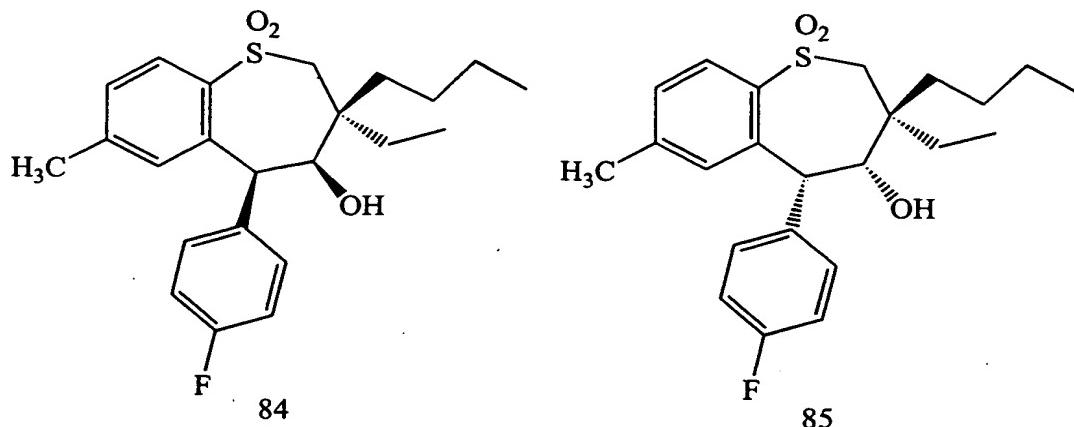
- [817] ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-morpholinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (83).



- [818] A mixture of 0.4 g (0.98 mmol) of compound 78 and 5.0 g (56 mmol) of morpholine was held at reflux for 2 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over $MgSO_4$. The ether solution was concentrated in vacuo. The residue was recrystallized from ether-hexanes to give compound 83, mp 176.5-187.5 °C.

[819] Example 45

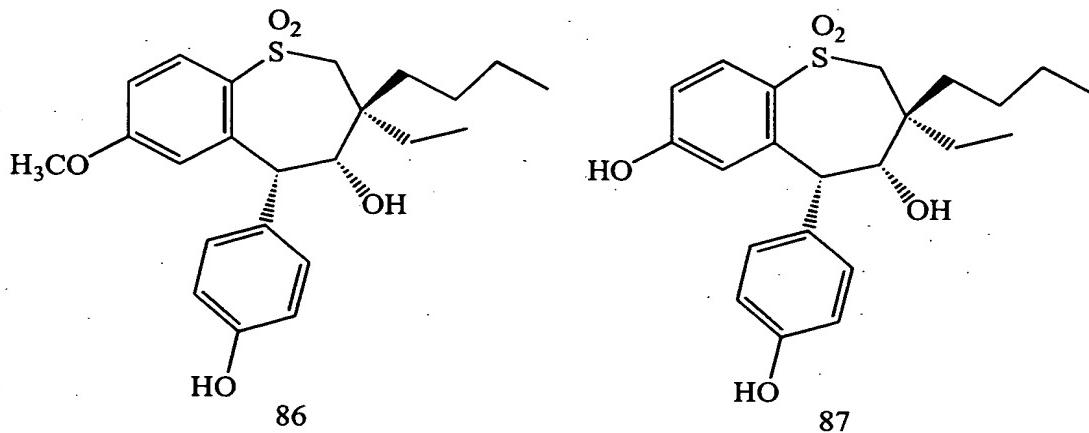
- [820] ($3\alpha,4\alpha,5\alpha$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (84), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-methyl-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (85).



[821] Alkylation of 4-methylphenol with 4-fluorobenzyl chloride according to the procedure described in J. Chem. Soc, 2431 (1958) gave 4-methyl-2-(4'-fluorobenzyl)phenol). This material was converted to compound 84 and compound 85 by the procedure similar to that in Example 18 method B.

[822] Example 46

[823] ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4-hydroxy-5-(4'-hydroxyphenyl)-7-methoxy-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (86), and ($3\alpha,4\beta,5\beta$) 3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-hydroxyphenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (87).

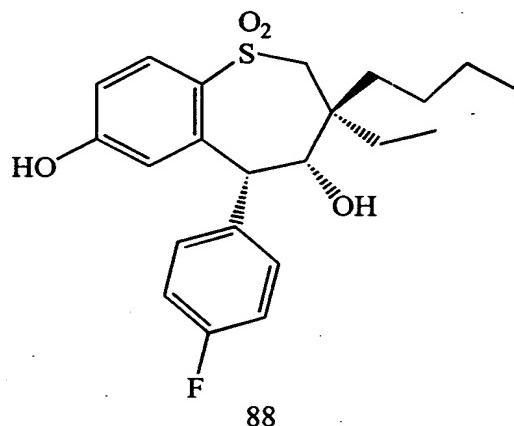


[824] To a solution of 0.52 (1.2 mmol) of compound 66 in 20 ml of methylene chloride was added 1.7 g (6.78 mmol) of born tribromide. The reaction mixture was cooled to -78°C and was stirred for 4 min. An additional 0.3 ml of boron tribromide was added to the reaction mixture and the reaction mixture was stirred

at -78°C for 1 h and quenched with 2 N HCl. The organic was extracted into ether. The ether layer was washed with brine, dried over MgSO₄, and concentrated in vacuo. The residue (0.48 g) was purified by HPLC (30% ethyl acetate in hexanes). The first fraction was 0.11 g of compound 86 as a white solid, mp 171.5-173 °C. The second fraction was crystallized from chloroform to give 0.04 g of compound 87 as a white solid, mp 264°C (dec).

[825] Example 47

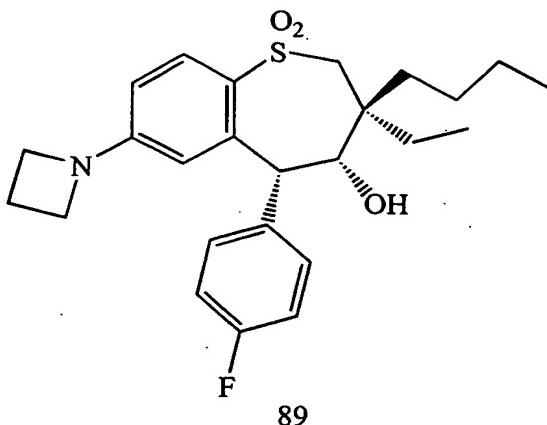
- [826] ($3\alpha,4\beta,5\beta$) **3-Butyl-3-ethyl-4,7-dihydroxy-5-(4'-fluorophenyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (88).**



- [827] Reaction of compound 70 with excess boron tribromide at room temperature and worked up as in Example 46 gave compound 88 after an HPLC purification.

[828] Example 48

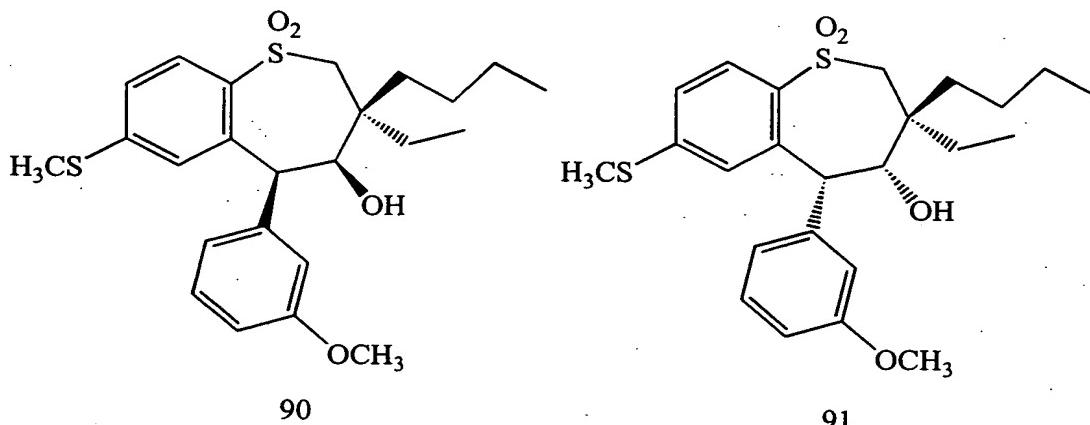
- [829] ($3\alpha,4\beta,5\beta$) **3-Butyl-3-ethyl-5-(4'-fluorophenyl)-4-hydroxy-7-(1-azetidinyl)-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (89).**



- [830] A mixture of 0.20 g (0.49 mmol) of compound 78, and 2.0 g (35 mmol) of aztidine was held at reflux for 3 h and concentrated in vacuo. The residue was diluted with ether (30 ml) and washed with water and brine and dried over MgSO₄. The ether solution was concentrated on a steam bath. The separated crystals were filtered to give 0.136 g of 89 as prisms, mp 196.5-199.5 °C.

[831] Example 49

- [832] (3 α ,4 α ,5 α) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (90). (3 α ,4 β ,5 β) 3-Butyl-3-ethyl-5-(3'-methoxyphenyl)-4-hydroxy-7-methylthio-2,3,4,5-tetrahydrobenzothiepine-1,1-dioxide (91).



- [833] A mixture of 0.4 g (0.95 mmol) of compound 79, 0.08 g (1.14 mmol) of sodium methanethiolate and 15 ml of anhydrous DMF was stirred at 60°C for 2 h. An additional 1.4 mmol of sodium methanethiolate was added to the reaction mixture